

Synthesis, characterization, and antimicrobial activities of novel double-armed benzo-15-crown-5 and their sodium and potassium complexes

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Abstract

New aldehyde- and halogen- (Cl, Br, I) substituted double-armed benzo-15-crown-5 derivatives are synthesized by the reactions of 4',5'-bis(bromomethyl)benzo-15-crown-5 with 5-chlorosalicylaldehyde, 5-bromosalicylaldehyde, or 5-iodosalicylaldehyde. The sodium and potassium complexes are obtained by reaction of crown ether with sodium perchlorate and potassium iodide, respectively. Novel Schiff base compounds containing three groups of benzo-15-crown-5 are obtained from the condensation of aldehydes with 4'-aminobenzo-15-crown-5. The structures of all compounds are elucidated by elemental analysis, ¹H, ¹³C NMR, IR, and mass spectra. The antifungal and antibacterial effects of the synthesized ligands are evaluated against pathogenic microorganisms and show varying degrees of inhibitory effects against the growth of different pathogenic strains.

Graphical abstract

Keywords

alkali metal complexes, antimicrobial activity, crown ethers, pathogenic microorganisms, Schiff bases

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Introduction

Crown ethers and their complexes have been the subject of significant interest for more than 50 years. Numerous types of macrocyclic ligands and their complexes have been synthesized, including crown ethers.^{1–6} Structurally, crown ethers are cyclic structures having a cavity that allows them to form stable complexes with metal ions.^{7–11} In particular, bis-crown ethers have superior selectivity for metal cations. Bis-crown compounds form intramolecular sandwich-type complexes with large metal cations (such as Cs⁺, Sr²⁺, Tl⁺, Ba²⁺).^{2,3,12} The flexible linker between both crown ether moieties provides better extraction efficiency, that is, good coordination ability, which increases the selectivity for the cations in solution. There are also examples of substituted crown ethers having different selectivity centers.^{6,13–15} The crown ether center can generate stable complexes with alkali metal and alkaline earth metal

cations, while the substituted side center can form transition metal complexes.^{12,16–23} Their complexing properties make crown ethers especially interesting and useful compounds in biological research and in chemistry.^{24–31} The ion complex-carrying ability of crown ethers results in them resembling natural ionophores (such as gramicidin). In this context, similar to natural ionophores, their ability to transport ions through lipid membranes by channeling has enabled the use of crown ethers in various biological applications.²⁷ In addition, bis-crown ether Schiff base derivatives and their sodium complexes have been shown to exhibit antibacterial activity against gram-positive and gram-negative bacteria.³²

Numerous examples can be found in the literature with bis-crown ether ligands and complexes, but up to now there have only been a few examples reported of tris-crown ethers.^{4,5} This prompted us to synthesize new ionophoric receptors containing more than one crown ether unit in

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their structure. Herein, we have designed and synthesized double-armed crown ethers possessing dialdehydes **1–3** (Scheme 1). Schiff base derivatives **4–6** having three benzo-15-crown-5 groups in which two benzo-15-crown-5 moieties are linked via a condensation reaction to the crown ether aldehydes **1–3** using 4'-aminobenzo-15-crown-5 (Scheme 2).

Results and discussion

Syntheses and structural characterizations

New substituted crown ethers **1–3** were successfully prepared in yields of 60%, 59%, and 73%, respectively. It was observed that the products **1–3** were soluble in solvents such as tetrahydrofuran (THF), acetonitrile, and methanol.

The novel Schiff bases **4–6** were obtained from the condensation reaction of two equivalents of 4'-aminobenzo-15-crown-5 with one equivalent of the aldehyde **1–3**.

The sodium **1a–3a** and potassium complexes **1b** and **3b** were prepared by reactions of new ligands **1–3** with NaClO₄ or KI (Scheme 1). The potassium complex of ligand **2** could not be obtained because the product could not be purified. Although the experiment was repeated several times, the complex was not obtained and the free ligand collapsed. Spectroscopic analyses showed that the stoichiometry of the sodium complexes was 1:1 (Na⁺:benzo-15-crown-5) and that of the potassium complexes was 1:2 (K⁺:benzo-15-crown-5). Sandwich complexes are an expected structural feature for potassium complexes **1b** and **3b**. Because potassium cation is too large to fit into the benzo-15-crown-5 cavity, in these complexes, K⁺ ion is coordinated by ten 15-crown-5 oxygen atoms. However, Na⁺ ion is smoothly fit into the 15-crown-5 cavity. The solubility of the complexes was very low.

The structures of the solid crown ether ligands **1–6** and complexes **1a–3a**, **1b**, and **3b** are confirmed from their ¹H, ¹³C NMR, IR, and mass spectral data. In addition, all of the new substituted crown ethers **1–3** and Schiff bases **4–6** were investigated for their antimicrobial activity against the pathogenic bacterial strains *Bacillus cereus*, *Listeria monocytogenes*, *Micrococcus luteus*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Salmonella typhi* H, *Escherichia coli*, *Enterobacter aerogenes*, *Sh. dysenteriae* type 2, and for their antifungal activity against *Candida albicans*.

Fourier-transform infrared spectroscopy spectra

The Fourier-transform infrared spectroscopy (FTIR) spectra of all the compounds displayed strong stretching bands between 1016 and 1145 cm⁻¹ attributed to the (C–O–C) bond of the crown ether ring. The spectra of the crown aldehydes **1–3** show the broad, strong bands at 1682, 1680, and 1676 cm⁻¹ for the carbonyl group (C=O) vibration. In the IR spectra of new imine compounds **4–6**, the C=N–stretching vibrations were detected at 1614, 1612, and 1614 cm⁻¹, respectively. The absence of peaks due to the

carbonyl groups belonging to compounds **1–3** also supported the successful obtaining imine bond. The (C–O–C) aromatic and aliphatic stretching vibrational modes were detected as broad peaks upon complexation in **1a–3a**. The characteristic, wide, and very strong bands observed at 1097, 1068, and 1078 cm⁻¹ provide good evidence of the presence of perchlorate in the sodium complexes **1a–3a**. The IR spectra of potassium complexes **1b** and **3b** are similar to the ligand spectra, but small shifts were detected on complex formation (see the 'Experiment' section).

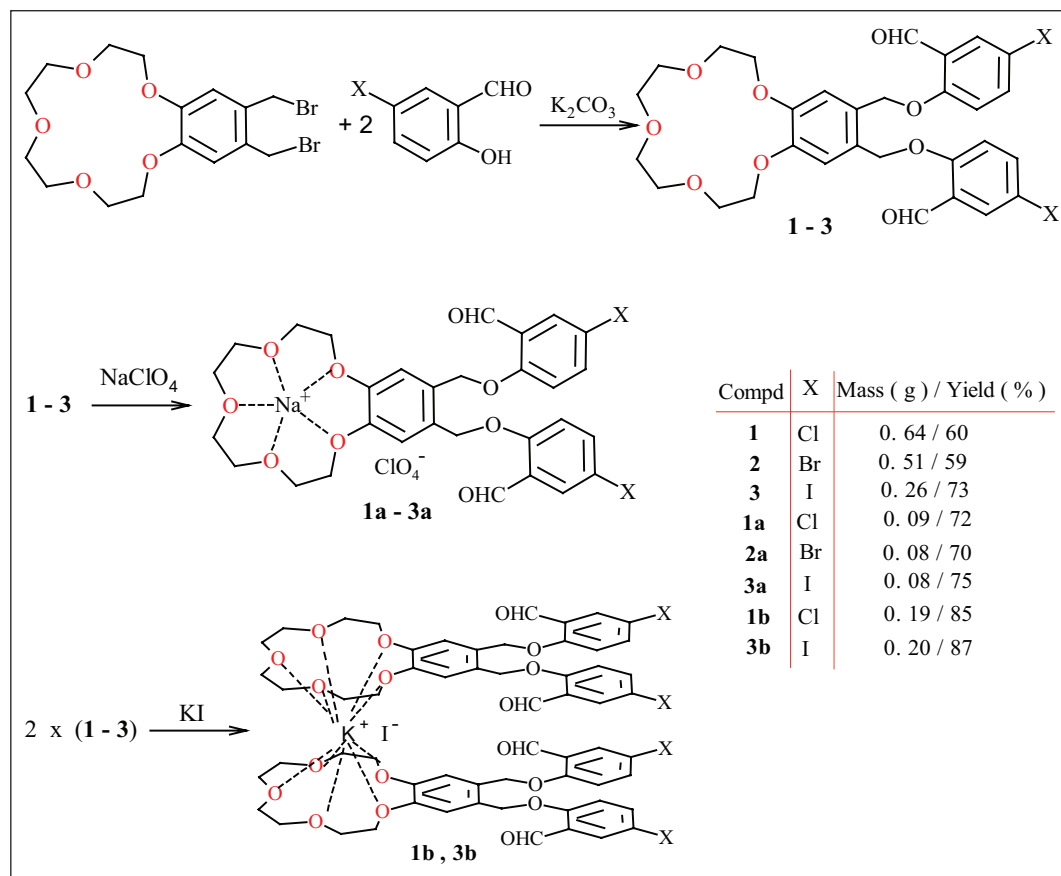
¹H and ¹³C NMR spectra

As expected, the structures of compounds **1–6** and complexes **1a–3a** and **1b**, **3b** in solution are symmetrical (see Figure 1).

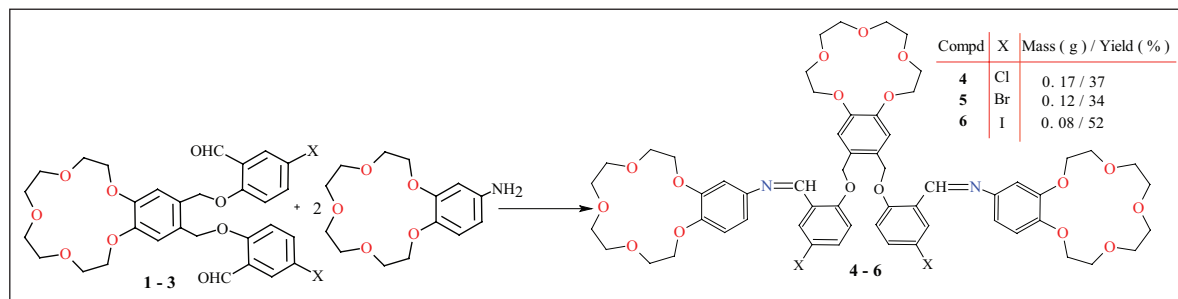
In the ¹H NMR spectra of crown ether compounds **1–3** and their complexes **1a–3a** and **1b**, **3b**, characteristic peaks ascribable to the –CHO protons were evident. These proton peaks (–CHO) were observed as singlets at 10.32, 10.12, and 10.26 ppm, respectively. For sodium complexes **1a–3a**, these peaks were observed as singlets at 10.21, 10.11, and 10.06 ppm, and for potassium complexes **1b** and **3b**, at 10.28 and 10.22 ppm, respectively. The benzylic protons (Ph–OCH₂–) for compounds **1–3** were seen as singlets at 5.17, 5.31, and 5.15 ppm, respectively. The crown ether units were evident at 3.41–4.78 ppm with the appropriate integrations. The crown ether proton peaks of sodium complexes **1a–3a** in the form of perchlorate salts to a slight shift in comparison with the free ligands. As a result of cation bonding to the crown ether moieties, downfield shifts of the proton peak resonances were observed due to the electron-withdrawing effects of the cation. However, the crown ether proton peaks of the potassium complexes showed slightly upfield shifts. That is unexpected and may be due to the ring current effect resulting from π -stacking in the sandwich complex of the 15-crown-5 moieties upon K⁺ ion binding. A similar situation in a related sandwich structure has been observed and reported.³³ The chemical shifts of the aromatic and crown ether protons in compound **3** and potassium complex **3b** are shown in Figure 2. The most significant changes in the spectra were found for the proton signals of the methylene (–OCH₂–CH₂O–) groups of the crown ether moiety.

The ¹H NMR spectra of tritopic Schiff bases **4–6** contain signals for the characteristic azomethine protons (HC=N) at 8.74, 8.73, and 8.68 ppm, respectively. The absence of carbonyl groups belonging to crown ether aldehydes **1–3** also support the formation of obtaining imine bond **4–6**. Additional support for the formation of Schiff bases **4–6** was provided (Figure 3), as the addition of second crown ether ring to the compounds **1–3** causes changes in the chemical shift of the methylene group of the crown ether (–OCH₂–CH₂O–) peak.

In ¹³C NMR, the signals of the carbonyl carbons (C-15) in compounds **1–3** were present at 188.0, 188.3, and 187.7 ppm, respectively. However, quite different chemical shifts (126.6, 115.7, and 83.7 ppm) were detected for the C-12 carbons of **1–3**. This can be explained by the changing



Scheme 1. Synthesis of new crown ether aldehydes (**1–3**) and complexes (**1a–3a** and **1b, 3b**).



Scheme 2. Synthesis of tris-crown ether Schiff bases (**4–6**).

of the electronegativity from Cl, Br to I. While the electronegativities of the halogens bound to the C-12 carbon make significant changes in the chemical shift of this carbon, the C-15 carbon was less affected by the electronegativities of the halogens and therefore small differences were observed between the chemical shifts. The signals of the four 15-crown-5 carbons ($-\text{OCH}_2\text{CH}_2\text{O}-$) and aromatic carbon peaks indicated that compounds **1–3** are symmetric.

Due to the additional crown ring for compounds **4–6**, more than four resonances were observed in the crown ether peak region. The absence of carbonyl carbons belonging to crown ether aldehydes **1–3** and the observed imine carbons ($-\text{HC}=\text{N}-$) at 156.6, 158.1, and 157.9 ppm support the formation of Schiff bases **4–6**.

In the ^{13}C NMR spectra of the complexes **1a–3a**, **1b**, and **3b**, small chemical shifts observed for all the peaks result

from interactions of the 15-crown-5 oxygen atoms with the sodium or potassium cations. The spectra indicate that new complexes had formed.

Mass spectra

The mass spectra of the synthesized crown aldehydes **1–3** and Schiff bases **4–6** are given in Table 1. The mass spectra of the all compounds were obtained by the API-ES technique. In these spectra, the ligand plus sodium ($[\text{M} + \text{Na}]^+$) peaks were observed as molecular ion peaks for all of the substituted crown ethers **1–3** and Schiff bases **4–6**. Adduct formation, either with sodium or potassium cations, is frequently observed in mass spectra for crown ethers.³⁴ Actually, the majority of observed ions in the mass spectra of crown ethers are adduct ions or pseudomolecular ions

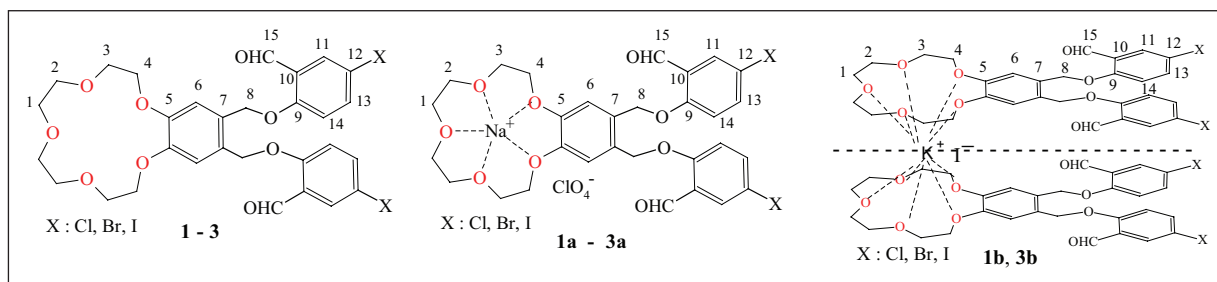


Figure 1. Numbering of the crown ether carbons and protons.

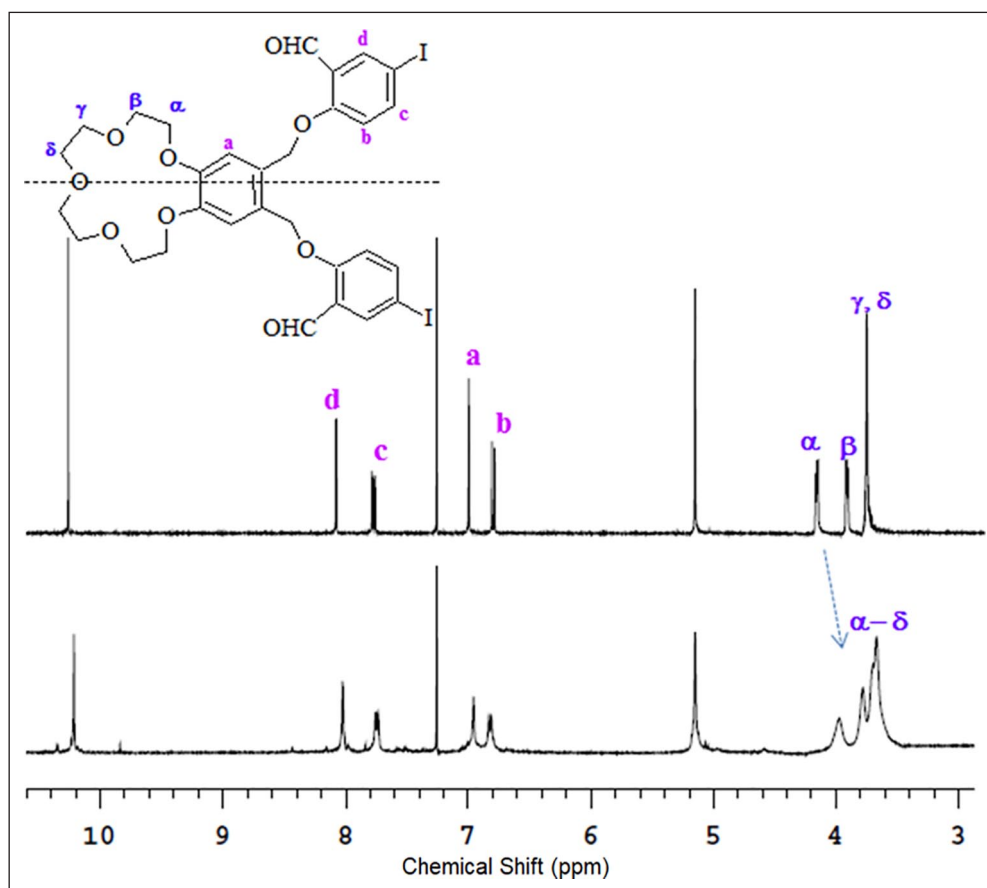


Figure 2. ¹H NMR spectral changes of the crown ether (–OCH₂–CH₂O–) and aromatic protons of free ligand **3** and potassium complex **3b**—in CDCl₃.

(e.g. [M + H]⁺, [M + NH₄]⁺, [M + Na]⁺ or [M + K]⁺).^{34–36} The isotope atoms of chlorine and bromine giving rise to M + 2 and M + 4 peaks (compounds **1**, **2**, **4**, and **5**). In the mass spectra of **1–3**, the dominant peaks at *m/z* 627 (100%), 717 (100%), and 811 (100%) correspond to [M + Na]⁺ (for compounds **1** and **3**) and [M + 2 + Na]⁺ (for compound **2**). The molecular ion peak for the ligand plus sodium ([M + Na]⁺) for Schiff bases **4–6** was detected at *m/z* 1157 (26%), 1245 (26%), and 1341 (71%), respectively.

The mass spectra of the synthesized alkali metal complexes **1a–3a**, **1b**, and **3b** are given in Table 2. Sodium and potassium cations bind to the crown ether cavity by ion dipole interactions. In the mass spectra of the Na⁺ complexes **1a–3a**, molecular ion peaks corresponding to the ligand plus sodium appeared as expected ([M + Na]⁺).

The molecular ion peak [2M + K]⁺ of the potassium complexes **1b** and **3b** were detected at *m/z* 1247 and 1615. These peaks show that 1:2 (metal / ligand) complexes are formed. In addition [2M + 2 + K] and [2M + 4 + K] peaks confirm the existence of chlorine and bromine in complexes **1b** and **3b**.

Antimicrobial activity

All the newly synthesized compounds **1–6** and different antibiotics were found to be effective to various degrees toward the growth inhibition of different pathogenic strains (Figure 4). The results of the antibacterial screening showed that compound **1** had activity (diameter of zone inhibition: 25 mm) against most strains of the gram-positive and

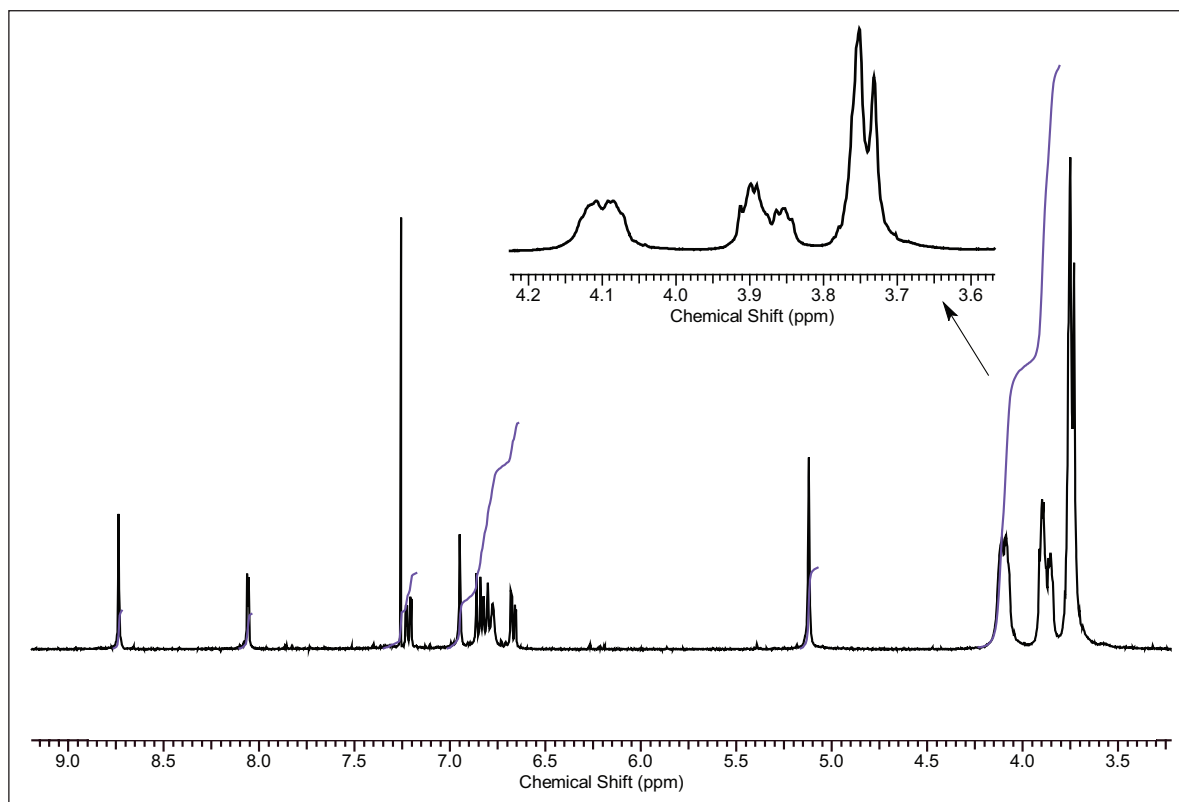


Figure 3. ^1H NMR spectrum of compound **4** and the appearance of the crown ether proton peaks ($-\text{OCH}_2-\text{CH}_2\text{O}-$) and aromatic protons—in CDCl_3 .

Table 1. The mass spectral data of crown ether aldehydes **1–3** and Schiff bases **4–6**.

Compound	Calculated	Found	Ion; % abundance
1	$[\text{M}]^+$: 604	627	$[\text{M} + \text{Na}]^+$; 100
		628	$[\text{M} + \text{Na} + \text{H}]^+$; 63
		629	$[\text{M} + 2 + \text{Na}]^+$; 54
		631	$[\text{M} + 4 + \text{Na}]^+$; 11
2	$[\text{M}]^+$: 692	715	$[\text{M} + \text{Na}]^+$; 52
		716	$[\text{M} + \text{Na} + \text{H}]^+$; 77
		717	$[\text{M} + 2 + \text{Na}]^+$; 100
		719	$[\text{M} + 4 + \text{Na}]^+$; 54
3	$[\text{M}]^+$: 788	811	$[\text{M} + \text{Na}]^+$; 100
		812	$[\text{M} + \text{Na} + \text{H}]^+$; 36
4	$[\text{M}]^+$: 1134	1157	$[\text{M} + \text{Na}]^+$; 26
		1158	$[\text{M} + \text{Na} + \text{H}]^+$; 31
		1159	$[\text{M} + 2 + \text{Na}]^+$; 19
		1161	$[\text{M} + 4 + \text{Na}]^+$; 11
5	$[\text{M}]^+$: 1222	306	$[\text{C}_{14}\text{H}_{19}\text{NO}_5 + \text{Na} + 2\text{H}]^+$; 100
		1245	$[\text{M} + \text{Na}]^+$; 26
		1246	$[\text{M} + \text{Na} + \text{H}]^+$; 77
		1247	$[\text{M} + 2 + \text{Na}]^+$; 58
		1249	$[\text{M} + 4 + \text{Na}]^+$; 35
6	$[\text{M}]^+$: 1318	490	$[\text{C}_{21}\text{H}_{23}\text{BrNO}_5 + \text{CH}_3\text{CN} - \text{H}]^+$; 100
		1359	$[\text{M} + \text{CH}_3\text{CN}]^+$; 81
		1341	$[\text{M} + \text{Na}]^+$; 71
		1273	$[\text{M} - \text{C}_2\text{H}_5\text{O}]^+$; 100

gram-negative bacteria (*M. luteus*, *E. aerogenes*) tested. Compound **2** showed activity against the strains *B. cereus* and *S. epidermidis* (26 and 25 mm).

Salmonella typhi H, *Sh. dysenteriae* type 2 (*Sh. dys. type* 2), and *S. epidermis* are pathogenic microorganisms, and

these microorganisms are gaining resistance to conventional antibiotics day by day.³⁷ Therefore, there is a need for new antibiotics effective against these pathogenic microorganisms. Compound **3** showed greater activity against *S. typhi* H, *Sh. dys. type* 2, and *S. epidermis* (30, 20, and 30 mm,

Table 2. The mass spectral data of the sodium and potassium complexes **1a–3a**, **1b**, and **3b**.

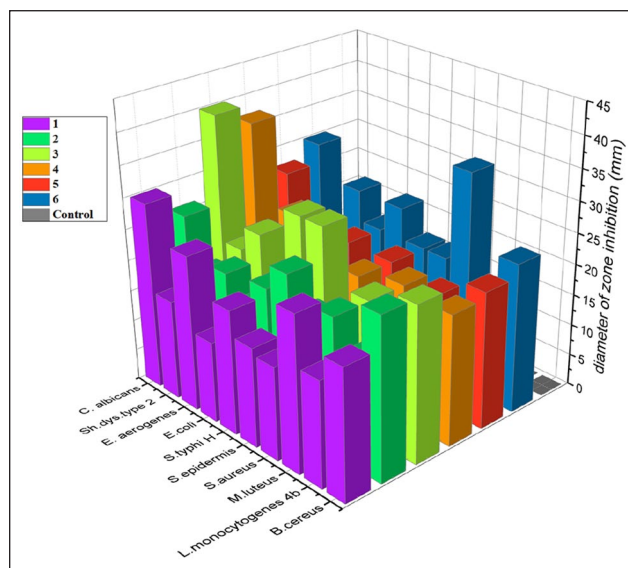
Compound	Calculated	Found	Ion; % abundance
1a	$[M + Na]^+$: 627	627	$[M + Na]^+$; 100
		628	$[M + Na + H]^+$; 51
		629	$[M + 2 + Na]^+$; 55
		631	$[M + 4 + Na]^+$; 18
2a	$[M + Na]^+$: 715	715	$[M + Na]^+$; 100
		716	$[M + Na + H]^+$; 62
		717	$[M + 2 + Na]^+$; 71
		719	$[M + 4 + Na]^+$; 34
3a	$[M + Na]^+$: 811	811	$[M + Na]^+$; 100
		812	$[M + Na + H]^+$; 47
1b	$[2M + K]^+$: 1247	1247	$[2M + K]^+$; 100
		1248	$[2M + K + H]^+$; 33
		1249	$[2M + 2 + K]^+$; 21
		1251	$[2M + 4 + K]^+$; 16
3b	$[2M + K]^+$: 1615	1615	$[2M + K]^+$; 28
		1616	$[2M + K + H]^+$; 100

respectively) than conventional antibiotics such as amoxycillin and sulphamethoxazole. Schiff base **4** showed the most activity against *M. luteus*, *B. cereus*, *S. epidermis*, and *E. aerogenes* (22, 21, 20, and 25 mm, respectively). Compound **5** showed the most activity against *B. cereus* and *E. aerogenes* (22 mm). Compound **6** showed the best activity against *M. luteus*, *S. typhi* H, and *E. aerogenes* (35, 25, and 25 mm, respectively). The change in the electronegativities of halogens did not cause a standard change in the biological activities of the synthesized compounds (**1–6**).

It is known that *C. albicans* showing pathogenicity in human fungal infections causes significant morbidity and mortality in immunocompromised patients (AIDS, cancer chemotherapy, organ, or bone transplantation).³⁸ All the synthesized compounds **1–6** demonstrated effective action against this fungus. In particular, compounds **3** and **4** showed the best inhibitory activity against *C. albicans*, with inhibition zone values of 40 and 37 mm, respectively.

Conclusion

In conclusion, a series of new crown ether compounds containing halogen (Cl, Br, or I), aldehyde, and imine groups have been synthesized. Aldehyde crown ethers **1–3** were synthesized by the reaction of 4',5'-bis(bromomethyl)benzo-15-crown-5 with substituted salicylaldehyde derivative in the presence of K_2CO_3 . Three crown ether Schiff bases were obtained by the reaction of 4'-aminobenzo-15-crown-5 with the corresponding crown ether aldehydes **1–3**. Sodium complexes **1a–3a** and potassium complexes **1b** and **3b** of the crown ether aldehydes were also synthesized using $NaClO_4$ and KI. The molecular structures of the newly synthesized ligands **1–6** and complexes **1a–3a**, **1b**, and **3b** were identified from their analytical and spectral data. In this study, compounds **1–6** and their in vitro antimicrobial properties were evaluated against several pathogenic bacteria and *C. albicans*. From these antimicrobial studies, it was observed that the antibacterial and antifungal activities of the new compounds were moderate to good. The antimicrobial



Positive cont	<i>S. aureus</i>	<i>P. putida</i>	<i>E. coli</i>	<i>S. typhi</i> H	<i>Br. abortus</i>	<i>C. albicans</i>
K3025	14	25	20	-	-	-
SXT25	24	18	18	17	-	-
AMP10	30	8	10	11	-	-
AMC30	30	15	14	19	-	-
NYS100	-	-	-	-	-	20

SXT25, Sulphamethoxazole (25 µg); AMP10, Ampicillin (10 µg); NYS100, Nystatin (100 µg); K30, Kanamycin (30 µg); AMC30, Amoxycillin (30 µg).

Figure 4. Biological activity of compounds **1–6** and standard reagents (diameter of zone inhibition (mm)).

activities of the novel compounds were compared with the seven commercial antibiotics and the synthesized compounds were found to be as effective as the tested antibiotics.

Experiment

Reagents and equipments

The starting materials, tetraethylene glycol dichloride, benzo-15-crown-5, and 4',5'-bis(bromomethyl)benzo-15-crown-5 were prepared according to the literature.^{39–41} 4'-Aminobenzo-15-crown-5, 5-chlorosalicylaldehyde, 5-bromosalicylaldehyde, and 5-iodosalicylaldehyde were purchased commercially from Aldrich and used without any further purification. All the solvents (dimethylformamide (DMF), THF, and EtOH) were purified and dried by standard procedures. The perchlorate salts of sodium complexes with organic ligands are potentially explosive and strong oxidizing, which means they help other materials burn. Due to the increased explosion potential, extreme caution should be exercised when working with perchlorate salts. The measurement of melting points was determined on a Gallenkamp melting point apparatus. The IR spectra were recorded using a Shimadzu Infinity model FTIR spectrometer equipped with an attenuated total reflectance (ATR) attachment. ^1H and ^{13}C NMR spectra were recorded with a Varian Mercury, high-performance

Digital FT-NMR (400 MHz) spectrometer (chemical shift values are expressed in ppm, SiMe₄ as an internal standard). Mass spectra were obtained using a Waters 2695 Alliance Micromass ZQ LC/MS spectrometer. The content of carbon, hydrogen, and nitrogen in all compounds was determined on a LECO CHNS-932 elemental analyzer.

Detection of antimicrobial activity

Staphylococcus aureus ATCC25923, *Staphylococcus epidermidis* ATCC12228, *Micrococcus luteus* ATCC9341, *Bacillus cereus* RSKK-863, *Listeria monocytogenes* 4b ATCC19115, *Salmonella typhi* H NCTC901.8394, *Enterobacter aerogenes* sp., *Escherichia coli* ATCC1280, *Sh. dysenteriae* type 2 sp. were used as pathogenic bacterial cultures and *C. albicans* Y-1200-NIH was used as a fungal agent. The antimicrobial activities of the synthesized compounds **1–6** were examined by the well-diffusion method against five gram-positive bacteria (*S. aureus*, *S. epidermidis*, *M. luteus*, *B. cereus*, *L. monocytogenes* 4b) and four gram-negative bacteria (*S. typhi* H, *E. aerogenes*, *E. coli*, *Sh. dys.* type 2) and yeast (*C. albicans*).³⁷

The synthesized new compounds were dissolved (10³ µM) in DMF (DMF was used as a solvent because it had no antimicrobial activity against any of the tested organisms). 1% (v/v) of the 24-h broth culture (pathogenic microorganisms) containing 106 CFU/mL was placed in sterile Petri dishes. Mueller-Hinton Agar (MHA) (15 mL), which was then maintained at 45 °C, was poured into a Petri dish and allowed to solidify slowly. The 6-mm-diameter wells were then carefully punched using a sterile cork borer and filled fully with the synthesized compounds. The plates were incubated for 24 h at 37 °C. At the end of this period, the mean value obtained for the two wells was used to calculate the zone of growth inhibition of each compound. Pathogenic bacterial cultures and yeast were investigated for resistance to five antibiotics (ampicillin, nystatin, kanamycin, sulphamethoxazole, and amoxycillin) produced by Oxoid Ltd., Basingstoke, UK.

Synthesis of compounds

General method for the preparation of crown ether aldehydes **1–3**

To the corresponding salicylaldehyde (5-chlorosalicylaldehyde, 5-bromosalicylaldehyde, or 5-iodosalicylaldehyde) (3.5 mmol) dissolved in DMF (20 mL), K₂CO₃ (3.5 mmol) was added, and the reaction mixture was left to stir overnight at room temperature. While stirring, a solution of 4',5'-bis(bromomethyl)benzo-15-crown-5 (1.75 mmol) in DMF (20 mL) was added dropwise and then the reaction was left to stir for 36 h at 110 °C under reflux. The consumption of the starting compounds was monitored by thin-layer chromatography (TLC) (silica, eluent; THF). Water was then added until the reaction solution became cloudy. The resulting precipitate was filtered off. The crude or pure product was recrystallized from THF/methanol (10:1).

2,2'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis(methyleneoxy)]bis(5-chlorobenzaldehyde) **1**: M.p.: 123 °C; IR (KBr) cm⁻¹:

2914 (C–H)_{aliph}, 1682 (C=O), 1595 (C=C), 1273–1215 (C–O–C)_{arom}, 1128, 1066 (C–O–C)_{aliph}; ¹H NMR (400 MHz, CDCl₃): δ = 3.75–4.15 (8H, m, –OCH₂CH₂O–), 5.17 (2H, s, Ph–CH₂O–), 6.97 (1H, d, *J* = 8.8 Hz, H-14), 7.00 (1H, s, H-6), 7.46 (1H, dd, *J* = 8.8 Hz, *J* = 2.7 Hz, H-13), 7.77 (1H, d, *J* = 2.7 Hz, H-11), 10.32 (1H, s, –CHO); ¹³C NMR (400 MHz, CDCl₃): δ = 68.8 (C-8), 69.2, 69.4, 70.4, 71.0 (C-1-4), 114.5 (C-6), 115.3 (C-14), 125.9 (C-10), 126.6 (C-12), 126.7 (C-7), 127.0 (C-11), 135.5 (C-13), 149.4 (C-5), 159.0 (C-9), 187.9 (C-15); Anal. calcd for C₃₀H₃₀Cl₂O₉ (605.46): C, 59.51; H, 4.99; found: C, 59.28; H, 5.02.

2,2'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis(methyleneoxy)]bis(5-bromobenzaldehyde) **2**: M.p.: 151 °C; IR (KBr) cm⁻¹: 2937 (C–H)_{aliph}, 1680 (C=O), 1589 (C=C), 1273–1234 (C–O–C)_{arom}, 1122, 1064 (C–O–C)_{aliph}; ¹H NMR (400 MHz, DMSO-*d*₆): δ = 3.61–4.09 (8H, m, –OCH₂CH₂O–), 5.31 (2H, s, Ph–CH₂O–), 7.32 (1H, s, H-6), 7.37 (1H, d, *J* = 8.9 Hz, H-14), 7.71 (1H, d, *J* = 2.8 Hz, H-11), 7.79 (1H, dd, *J* = 8.9 Hz, *J* = 2.8 Hz, H-13), 10.12 (1H, s, CHO); ¹³C NMR (400 MHz, DMSO-*d*₆): δ = 68.7 (C-8), 69.0, 69.1, 70.0, 70.7 (C-1-4), 113.0 (C-6), 115.7 (C-12), 117.2 (C-14), 126.4 (C-10), 127.6 (C-7), 130.7 (C-13), 138.7 (C-11), 148.6 (C-5), 160.0 (C-9), 188.3 (C-15); Anal. calcd for C₃₀H₃₀Br₂O₉ (694.36): C, 51.89; H, 4.35; found: C, 51.52; H, 4.10.

2,2'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis(methyleneoxy)]bis(5-iodobenzaldehyde) **3**: M.p.: 156 °C; IR (KBr) cm⁻¹: 2921 (C–H)_{aliph}, 1676 (C=O), 1583 (C=C), 1271–1234 (C–O–C)_{arom}, 1118, 1045 (C–O–C)_{aliph}; ¹H NMR (400 MHz, CDCl₃): δ = 3.75–4.16 (8H, m, –OCH₂CH₂O–), 5.15 (2H, s, Ph–CH₂O–), 6.79 (1H, d, *J* = 8.8 Hz, H-14), 7.00 (1H, s, H-6), 7.77 (1H, dd, *J* = 8.8 Hz, *J* = 2.7 Hz, H-13), 8.08 (1H, d, *J* = 2.7 Hz, H-11), 10.26 (1H, s, –CHO); ¹³C NMR (400 MHz, CDCl₃): δ = 68.6 (C-8), 69.2, 69.4, 70.4, 71.1 (C-1-4), 83.7 (C-12), 110.0 (C-10), 115.3 (C-14), 115.4 (C-6), 126.7 (C-7), 137.7 (C-11), 144.2 (C-13), 149.4 (C-5), 160.1 (C-9), 187.7 (C-15); Anal. calcd for C₃₀H₃₀I₂O₉ (788.36): C, 45.71; H, 3.84; found: C, 45.34; H, 3.74.

General method for the preparation of sodium complexes **1a–3a**

To a stirred solution of crown ether aldehydes (**1–3**) (0.16 mmol) in methanol (15 mL) was added NaClO₄ (0.16 mmol) and the reaction mixture was heated for 2 h. A white solid was obtained that was then filtered, washed with methanol and diethyl ether, and dried at room temperature.

2,2'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis(methyleneoxy)]bis(5-chlorobenzaldehyde) sodium complex (**1a**): M.p.: 175 °C; IR (KBr) cm⁻¹: 2917 (C–H)_{aliph}, 1680 (C=O), 1593 (C=C), 1269–1225 (C–O–C)_{arom}, 1126, 1045 (C–O–C)_{aliph}, 1097 (ClO₄); ¹H NMR (400 MHz, DMSO-*d*₆): δ = 3.59–4.06 (8H, m, –OCH₂CH₂O–), 5.30 (2H, s, Ph–CH₂O–), 7.04 (1H, s, H-6), 7.13 (1H, d, *J* = 8.9 Hz, H-14), 7.53 (1H, dd, *J* = 8.9 Hz, *J* = 2.4 Hz, H-13), 7.74 (1H, d, *J* = 2.7 Hz, H-11), 10.21 (1H, s, –CHO); ¹³C NMR (400 MHz, CDCl₃): δ = 68.5 (C-8), 69.0, 69.3, 70.2, 70.7 (C-1-4), 114.1 (C-6),

116.6 (C-14), 119.2 (C-12), 125.6 (C-10), 127.3 (C-7), 132.4 (C-13), 136.2 (C-11), 149.0 (C-5), 159.4 (C-9), 187.6 (C-15); Anal. calcd for $C_{30}H_{30}Cl_3O_{13}Na$ (727.90): C, 49.50; H, 4.15; found: C, 49.88; H, 4.38.

2,2'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis(methyleneoxy)]bis(5-bromobenzaldehyde) sodium complex (2a): M.p.: 194 °C; IR (KBr) cm^{-1} : 2968 (C-H)_{aliph}, 1680 (C=O), 1589 (C=C), 1273–1215 (C–O–C)_{arom}, 1145, 1016 (C–O–C)_{aliph}, 1068 (ClO₄); ¹H NMR (400 MHz, DMSO-*d*₆): δ=3.59–4.07 (8H, m, –OCH₂CH₂O–), 5.29 (2H, s, Ph–CH₂O–), 7.22 (1H, s, H-6), 7.31 (1H, d, *J*=8.9 Hz, H-14), 7.69 (1H, d, *J*=2.4 Hz, H-11), 7.76 (1H, dd, *J*=8.9 Hz, *J*=2.4 Hz, H-13), 10.11 (1H, s, –CHO); ¹³C NMR (400 MHz, DMSO-*d*₆): δ=68.3 (C-8), 68.4, 68.6, 69.5, 70.2 (C-1-4), 112.6 (C-6), 115.3 (C₁₂), 116.7 (C-14), 125.9 (C-10), 127.2 (C-7), 130.2 (C-13), 138.2 (C-11), 148.2 (C-5), 159.4 (C-9), 187.9 (C-15); Anal. calcd for $C_{30}H_{30}Br_2ClO_{13}Na$ (816.80): C, 44.11; H, 3.70; found: C, 44.24; H, 3.49.

2,2'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis(methyleneoxy)]bis(5-iodobenzaldehyde) sodium complex (3a): M.p.: 220 °C; IR (KBr) cm^{-1} : 2958 (C-H)_{aliph}, 1678 (C=O), 1585 (C=C), 1276–1234 (C–O–C)_{arom}, 1101, 1053 (C–O–C)_{aliph}, 1078 (ClO₄); ¹H NMR (400 MHz, DMSO-*d*₆): δ=3.59–4.06 (8H, m, –OCH₂CH₂O–), 5.27 (2H, s, Ph–CH₂O–), 7.16 (1H, d, *J*=8.9 Hz, H-14), 7.21 (1H, s, H-6), 7.84 (1H, d, *J*=2.4 Hz, H-11), 7.89 (1H, dd, *J*=8.9 Hz, *J*=2.4 Hz, H-13), 10.06 (1H, s, –CHO); ¹³C NMR (400 MHz, DMSO-*d*₆): δ=68.1 (C-8), 69.0, 69.1, 70.1, 70.5 (C-1-4), 83.6 (C-12), 109.8 (C-10), 114.9 (C-14), 115.1 (C-6), 126.1 (C-7), 137.1 (C-11), 143.2 (C-13), 148.9 (C-5), 159.5 (C-9), 187.5 (C-15); Anal. calcd for $C_{30}H_{30}I_2ClO_{13}Na$ (910.80): C, 39.56; H, 3.32; found: C, 38.96; H, 3.41.

General method for the preparation of potassium complexes **1b** and **3b**

Crown ether aldehyde **1** or **3** (0.16 mmol) and KI (0.08 mmol) were dissolved in methanol and the reaction mixture was heated for 2 h. A beige solid was obtained that was then filtered, washed with methanol and diethyl ether, and dried at room temperature.

2,2'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis(methyleneoxy)]bis(5-chlorobenzaldehyde) potassium complex (1b): M.p.: 146 °C; IR (KBr) cm^{-1} : 2912, 2876 (C-H)_{aliph}, 1678 (C=O), 1592 (C=C), 1270–1210 (C–O–C)_{arom}, 1122, 1056 (C–O–C)_{aliph}; ¹H NMR (400 MHz, CDCl₃): δ=3.72–4.01 (8H, m, –OCH₂CH₂O–), 5.23 (2H, s, Ph–CH₂O–), 7.01 (1H, s, H-6), 7.06 (1H, d, *J*=8.9 Hz, H-14), 7.70 (1H, d, *J*=2.4 Hz, H-11), 7.75 (1H, dd, *J*=8.9 Hz, *J*=2.4 Hz, H-13), 10.28 (1H, s, –CHO); ¹³C NMR (400 MHz, CDCl₃): δ=68.7 (C-8), 69.3, 69.4, 70.1, 70.2 (C-1-4), 114.9 (C-6), 115.0 (C-14), 125.9 (C-10), 126.9 (C-12), 127.2 (C-7), 128.7 (C-11), 135.6 (C-13), 148.4 (C-5), 159.9 (C-9), 188.0 (C-15); Anal. calcd for $C_{60}H_{60}Cl_4O_{18}KI$ (1376.92): C, 52.34; H, 4.39; found: C, 51.97; H, 4.14.

2,2'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis(methyleneoxy)]bis(5-iodobenzaldehyde) potassium complex (3b): M.p.:

248 °C; IR (KBr) cm^{-1} : 2942, 2864 (C-H)_{aliph}, 1686 (C=O), 1598 (C=C), 1287–1239 (C–O–C)_{arom}, 1112, 1096 (C–O–C)_{aliph}; ¹H NMR (400 MHz, CDCl₃): δ=3.51–4.02 (8H, m, –OCH₂CH₂O–), 5.15 (2H, s, Ph–CH₂O–), 6.96 (1H, s, H-6), 6.82 (1H, d, *J*=8.9 Hz, H-14), 7.74 (1H, dd, *J*=8.9 Hz, *J*=2.4 Hz, H-13), 8.02 (1H, d, *J*=2.4 Hz, H-11), 10.22 (1H, s, –CHO); ¹³C NMR (400 MHz, CDCl₃): δ=68.4 (C-8), 69.0, 69.6, 70.1, 70.9 (C-1-4), 86.1 (C-12), 109.0 (C-10), 115.2 (C-14), 115.7 (C-6), 127.3 (C-7), 138.1 (C-11), 144.0 (C-13), 149.1 (C-5), 160.1 (C-9), 186.7 (C-15); Anal. calcd for $C_{60}H_{60}I_2O_{18}K$ (1742.73): C, 41.35; H, 3.47; found: C, 41.53; H, 3.11.

General method for the preparation of Schiff bases **4–6**

To a solution of the corresponding crown ether aldehyde **1–3** (0.41 mmol) dissolved in ethanol (10 mL) was added and 4'-aminobenzo-15-crown-5 (0.82 mmol). The resulting reaction mixture was stirred under reflux for 8 h, then left to stand overnight at room temperature. The crude product was recrystallized from methanol.

N,N'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis[methyleneoxy(5-chloro-2,1-phenylene)(Z)methylylidene]]bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-amine) 4: M.p.: 112 °C; IR (KBr) cm^{-1} : 2920, 2864 (C-H)_{aliph}, 1614 (C=N), 1585 (C=C), 1263–1230 (C–O–C)_{arom}, 1128, 1051 (C–O–C)_{aliph}; ¹H NMR (400 MHz, CDCl₃): δ=3.73–4.11 (24H, m, –OCH₂CH₂O–), 5.12 (2H, s, Ph–CH₂O–), 6.66–8.02 (7H, m), 8.74 (1H, s); ¹³C NMR (400 MHz, CDCl₃): δ=68.69 (–OCH₂), 68.73–70.92 (–OCH₂CH₂O–), 108.56, 112.36, 111.23, 114.19, 114.26, 115.14, 126.67, 127.02, 127.24, 127.26, 131.85, 145.66, 147.93, 149.07, 152.66 (Ar-C), 156.65 (HC=N); Anal. calcd for $C_{58}H_{68}Cl_2O_{17}N_2$ (1136.07): C, 61.32; H, 6.03; N, 2.47; found: C, 61.30; H, 5.97; N, 2.73.

N,N'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis[methyleneoxy(5-bromo-2,1-phenylene)(Z)methylylidene]]bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-amine) 5: M.p.: 118 °C; IR (KBr) cm^{-1} : 2918, 2864 (C-H)_{aliph}, 1612 (C=N), 1587 (C=C), 1263–1229 (C–O–C)_{arom}, 1128, 1049 (C–O–C)_{aliph}; ¹H NMR (400 MHz, CDCl₃): δ=3.74–4.28 (24H, m, –OCH₂CH₂O–), 5.13 (2H, s, Ph–CH₂O–), 6.66–8.21 (7H, m), 8.73 (1H, s); ¹³C NMR (400 MHz, CDCl₃): δ=68.73 (–OCH₂), 68.87–71.12 (–OCH₂CH₂O–), 108.87, 112.60, 114.69, 115.89, 116.11, 121.66, 125.42, 124.01, 129.48, 129.71, 139.96, 145.93, 146.49, 146.97, 149.59 (Ar-C), 158.09 (HC=N); Anal. calcd for $C_{58}H_{68}Br_2O_{17}N_2$ (1224.97): C, 56.87; H, 5.60; N, 2.29; found: C, 56.71; H, 5.43; N, 2.57.

N,N'-[2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecine-15,16-diylbis[methyleneoxy(5-iodo-2,1-phenylene)(Z)methylylidene]]bis(2,3,5,6,8,9,11,12-octahydro-1,4,7,10,13-benzopentaoxacyclopentadecin-15-amine) 6: M.p.: 132 °C; IR (KBr) cm^{-1} : 2910, 2866 (C-H)_{aliph}, 1614 (C=N), 1585 (C=C), 1265–1213 (C–O–C)_{arom}, 1126, 1053 (C–O–C)_{aliph}; ¹H NMR (400 MHz, CDCl₃): δ=3.74–4.06 (24H, m, –OCH₂CH₂O–), 5.12 (2H, s, Ph–CH₂O–), 6.67–8.36 (7H, m), 8.68 (1H, s);

^{13}C NMR (400 MHz, CDCl_3): δ =68.30 ($-\text{OCH}_2-$), 68.53–71.02 ($-\text{OCH}_2\text{CH}_2\text{O}-$), 84.38, 102.54, 107.20, 114.18, 115.13, 117.28, 127.20, 127.43, 136.10, 136.40, 141.51, 140.74, 145.90, 149.72, 152.43 (Ar-C), 157.90 (HC=N); Anal. calcd for $\text{C}_{58}\text{H}_{68}\text{I}_2\text{O}_{17}\text{N}_2$ (1318.97): C, 52.82; H, 5.20; N, 2.12; found: C, 52.46; H, 5.13; N, 2.33.

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References

- Xia W-S, Schmehl RH, Li C-J, et al. *J Phys Chem B* 2002; 106: 833.
- Ushakov EN, Gromov SP, Fedorova OA, et al. *J Phys Chem A* 1999; 103: 11188.
- Edwin W, Konstantinos S, Mikio O, et al. *Bull Chem Soc Jpn* 1990; 63: 3670.
- Lee M, Zali-Boeini H, Li F, et al. *Tetrahedron* 2013; 69: 38.
- Xu X-D, Ou-Yang J-K, Zhang J, et al. *Tetrahedron* 2013; 69: 1086.
- Maher K and Mohammed S. *Oriental J Chem* 2018; 34: 1701.
- Gawley RE, Mao H, Haque MM, et al. *J Org Chem* 2007; 72: 2187.
- Zhang G, Zhang D, Zhou Y, et al. *J Org Chem* 2006; 71: 3970.
- Lodeiro C and Capelo JL. *J Incl Phenom Macro Chem* 2004; 49: 249.
- Douhal A and Roshal ADJA. *Chem Phys Lett* 2003; 381: 519.
- Szarmach M, Wagner-Wysiecka E, Fonari MS, et al. *Tetrahedron* 2012; 68: 507.
- Fedorov YV, Federova OA, Andryukhina EN, et al. *J Phys Org Chem* 2005; 18: 1032.
- Kruppa M, Mandl C, Miltschitzky S, et al. *J Am Chem Soc* 2005; 127: 3362.
- Yoo C, Dodge HM and Miller AJM. *Chem Commun* 2019; 55: 5047.
- Ouyang G-H, He Y-M, Li Y, et al. *Angew Chem* 2015; 54: 4334.
- Fedorova O, Lukovskaya E, Mizerev A, et al. *J Phys Org Chem* 2010; 23: 246.
- Tulyakova EV, Fedorova OA, Fedorov YV, et al. *J Phys Org Chem* 2008; 21: 372.
- Silva AP and McClenaghan ND. *Chem Eur J* 2002; 8: 4935.
- Bricks JL, Slominskii JL, Kudinova MA, et al. *J Photoch Photobio A Chem* 2000; 132: 193.
- Zhao L, Chen X, Guo F, et al. *J Lumin* 2014; 145: 486.
- Hayvali Z, Gündüz N, Kilic Z, et al. *Z Naturforsch B* 2000; 55: 975.
- Hayvali Z and Yardimci D. *Transition Met Chem* 2008; 33: 421.
- Hayvali Z. *Transition Met Chem* 2009; 34: 97.
- Kimura E. *Pure Appl Chem* 1989; 61: 823.
- Shamsipur M, Mizani F, Mousavi MF, et al. *Anal Chim Acta* 2007; 589: 22.
- Bubnis BP and Pacey GE. *Tetrahedron Lett* 1984; 25: 1107.
- Kralj M, Tusek-Bozic L and Frkanec L. *ChemMedChem* 2008; 3: 1478.
- Jagdale SD, Sawant AD and Deshmukh MB. *J Heterocycl Chem* 2017; 54: 161.
- Febles M, Montalvão S, Crespín GD, et al. *Bioorg Med Chem Lett* 2016; 26: 5591.
- Gokel G, Leevy W and Weber M. *Chem Rev* 2004; 104: 2723.
- Leevy WM, Donato GM, Ferdani R, et al. *J Am Chem Soc* 2002; 124: 9022.
- Hayvali Z, Güler H, Ögütçü H, et al. *Med Chem Res* 2014; 23: 3652.
- He X, Lam WH, Zhu N, et al. *Chem Eur J* 2009; 15: 8842.
- Koçoğlu S, Ogutcu H and Hayvali Z. *Res Chem Intermed* 2019; 45: 2403.
- Tong H, Bell D, Tabei K, et al. *J Am Soc Mass Spectrom* 1999; 10: 1174.
- Keller BO, Sui J, Young AB, et al. *Anal Chim Acta* 2008; 627: 71.
- Altundas A, Erdogan Y, Ogutcu H, et al. *Fresenius Environ Bull* 2016; 25: 5411.
- Teoh F and Pavelka N. *Pathogens* 2016; 5: 6.
- Calverley MJ and Dale J. *Acta Chem Scand B* 1982; 36: 241.
- Pedersen CJ. *J Am Chem Soc* 1967; 89: 7017.
- Winkler B, Mau AWH and Dai L. *Phys Chem Chem Phys* 2000; 2: 291.