



Investigation of photophysical behaviours and antimicrobial activity of novel benzo-15-crown-5 substituted coumarin and chromone derivatives

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ABSTRACT

Two different series of crown ether compounds (**4-11**) were synthesized by the reactions of 4',5'-bis(-bromomethyl)benzo-15-crown-5 (**3**) and 4'-amino-benzo-15-crown-5 with hydroxycoumarin and chromone derivatives. Coumarin-crown ether compounds (**4** and **5**) were synthesized by the reactions of 4',5'-bis(bromomethyl)benzo-15-crown-5 (**3**) with 4-hydroxycoumarin and 7-hydroxycoumarin. Chromone-crown ether compounds (**6-11**), were synthesized by the condensation reactions of 4'-amino-benzo-15-crown-5 with 3-formylchromone and 6-methyl-3-formylchromone in different solvent media. Sodium and potassium complexes (**4a-11a**, **4b-11b**) of new coumarin and chromone substituted benzo-15-crown-5 (B15C5) ligands (**4-11**) were prepared with NaSCN and KSCN, respectively. The syntheses of the novel crown ether compounds (**4-11**) and complexes (**4a-11a**, **4b-11b**) were elucidated by the elemental analysis, FTIR, ¹H NMR, ¹³C NMR and MS spectral data. The metal selectivities and effects of metal cations (Li⁺, Na⁺, K⁺, Mg²⁺, Ca²⁺, Ba²⁺, Ag⁺, Al³⁺, Cu²⁺, Zn²⁺, Ni²⁺, Pb²⁺, Fe³⁺, Cr³⁺) to the new crown ether compounds (**4-11**) were investigated by the absorption and fluorescence spectra. In addition, all of these substances were examined for antibacterial activity against pathogenic strains *Listeria monocytogenes* 4b, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* H, *Bacillus cereus*, *Micrococcus luteus*, *Shigella dysenteriae* type 2, *Staphylococcus epidermidis*, *Proteus vulgaris*, *Klebsiella pneumonia* sp., *Serratia marcescens* sp. and antifungal activity against *Candida albicans*.

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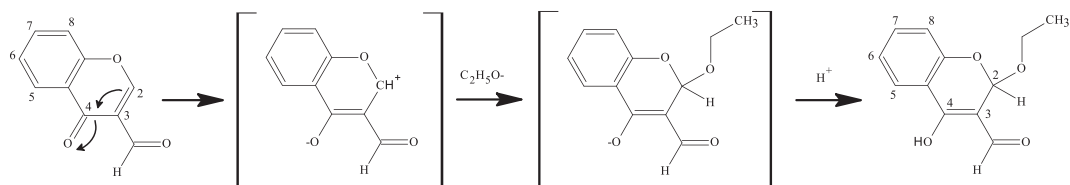
1. Introduction

The combination of a pyrone ring with a benzene ring gives rise to two distinct types benzopyrone ring. These rings are recognized namely benzo- α -pyrones called coumarines and benzo- γ -pyrones called chromones [1,2]. Coumarin compounds have been widely used in the fields of medicine, biology, cosmetic compounds and laser dyes [3,4]. Because, they have many important features including less toxicity effect, antibacterial and antitumor activities, high fluorescence quantum yield and large stokes shift [2,5–7]. Chromone compounds are abundant in nature product and they have a wide range of pharmacological properties like antiviral, antibacterial, antifungal, anticancer, anti-HIV and many other

activities. In addition, chromone derivatives occur in plant life, as a pigment in plant leaves and flower [8–10]. Among chromone derivatives are the 3-formylchromone (4-oxo-4H-1-benzopyran-3-carboxaldehyde), which possess three electronic centers (aldehyde carbon, highly reactive electrophilic carbon and carbonyl carbon) [11]. Generally, 3-formyl chromones with primary amines were given three types of products. One of them are those, which have condensation reactions so Schiff base compounds are obtained [12–17]. Another type of chromone products are 4-chromanone derivatives [18]. The third type of products are compounds in which weak γ -pyrone ring is broken and new compounds are occurred [15–17]. From the ¹H NMR, ¹³C NMR and elemental analyses, it was observed the addition of solvent (ethanolat anion) to a molecule of 3-formylchromone, phenomenon was also confirmed by crystallographic data and mass spectra [19,20]. The probable mechanism of the solvent addition to the pyrone ring is represented in Scheme 1.

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Scheme 1. The mechanism of the addition of an ethanolate-anion to the 3-formylchromone molecule.

Crown ethers are well known for their ability to form strong and stable complexes with alkaline and alkaline earth metals or organic cations, for which cavity size is a paramount factor [21,22]. Macrocyclic that possess ionophore ability has been a subject for extensive investigation not only for the synthetic protocol but also for its potential applications since its discovery by Pedersen [23]. Because of their complexation with metal ions, they are used as complexing agents, specific biosensor applications for specific antibodies, chemosensor applications, ion selective electrodes, photosensitivity systems, phase transfer catalysts and potential anti-cancer species [24–28]. Especially, design of fluorescent chemosensors is an important field for the analytical as well as environmental and biological problems, because chemical sensors based on ion-induced changes in fluorescence show high sensitivity and quick response to the toxic and precious metals [29–34]. Therefore, considerable efforts being made to develop selective fluorescence sensors for cation deduction. Two main types of fluorogenic chemosensors are based on the PET (Photoinduced Electron Transfer) and ICT (Internal Charge Transfer) mechanism [19,20]. Generally, in PET sensors the binding of the metal ion increases the fluorescence intensity. But spectral shifts are not observed in absorption and fluorescence spectra. ICT sensors, when complexed with metal cations, show a moderate increase in fluorescence intensity and significant shifts in UV visible and fluorescence spectra. As a result, the binding of metal cations reduces the donor power of the ionophore and can alter the ICT or PET process, causing changes in the absorption and/or fluorescence spectra. The situation that caused all these photophysical effects is due to the charge and the size of the cation [35,36].

In the present work, we report on the synthesis of novel coumarin and chromone substituted crown ethers and their alkali metal complexes (Na^+ , K^+) (Schemes 2–4). Compounds (4–11) and complexes (4a–11a, 4b–11b) was obtained and characterized by ^1H , ^{13}C NMR, FT-IR, MS spectroscopy, UV visible and fluorescence spectra. So in this article we synthesized new hybrid molecules (coumarin-substituted crown ether and chromone-substituted crown ether compounds), belonging to two different classes (crown ether and coumarin/chromone) of compounds. With their combined properties, these new compounds can have new applications. In this respect, *i*: absorption and fluorescence properties of 4–11 were recorded over range of concentration of added metal ions (Li^+ , Na^+ , K^+ , Mg^{2+} , Ca^{2+} , Ba^{2+} , Ag^+ , Al^{3+} , Cu^{2+} , Zn^{2+} , Ni^{2+} , Pb^{2+} , Fe^{3+} , Cr^{3+} , Co^{3+}). Synthesis of new fluorescent sensors for metal cation recognition is a versatile and growing field for ion-selective and sensitive materials. Furthermore, crown compounds can function as suitable synthetic model compounds which have similar functions for biological analogs, clearly discriminate different metal cations. *ii*. In this study we also wanted to determine the antimicrobial activities of new crown ether ligands and alkali metal complexes. The microorganisms used in this study were as follows: *Listeria monocytogenes* 4b, *Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi* H, *Bacillus cereus*, *Micrococcus luteus*, *Shigella dysenteriae* type 2, *Staphylococcus epidermidis*, *Proteus vulgaris*, *Klebsiella pneumonia* sp., *Serratia marcescens* sp. and antifungal activity against pathogenic yeast *Candida albicans*. This

antimicrobial activity study may help to understand the biological effects of new crown ether derivatives and thus to develop new antimicrobial agents based on new crown ether moieties.

2. Experimental

2.1. General

All solvents and all reagents were from Sigma Aldrich; all were used without further purification. NaSCN and KSCN salts were used for the synthesis of the alkali metal complexes of the compounds. Alkali, alkaline earth and transition metal cations were added to the solution as absorption and fluorescence reagents in the form of nitrate salts. Melting points were determined on a Gallenkamp melting point platform. ^1H and ^{13}C NMR spectra were recorded on a Bruker DPX FT-NMR (400 MHz) spectrometer (SiMe_4 as a internal standard). Chemical shifts for proton and carbon resonances were reported in ppm (δ). The IR spectra were detected using a Matson 1000 model FTIR spectrometer equipped a three-reflections ATR attachment. Carbon, nitrogen, hydrogen and sulfur analyses were performed on a LECO CHNS-932 elemental analyzer. Mass spectral data were performed on a Waters 2695 Alliance Micromass ZQ LC/MS and Agilent Technologies 6224 HRMS spectrometer. UV–visible spectra were recorded on a SHIMADZU UV-1800 UV–Vis spectrophotometer. Fluorescence spectra were recorded on a Perkin Elmer L555 Fluorescence Spectrometer.

2.2. Syntheses

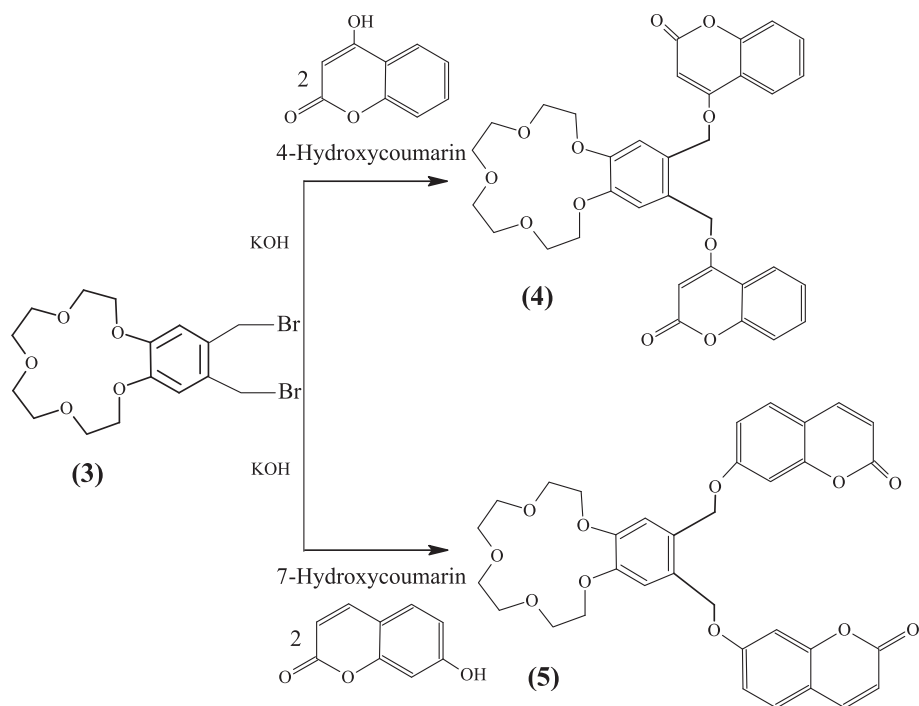
The starting compounds tetraethyleneglycoldichloride (1) [37], benzo-15-crown-5 (2) [38], and 4',5'-bis(bromomethyl)-benzo-15-crown-5 (3) [39] were prepared according to the cited procedure.

2.2.1. General procedure for the synthesis of coumarin compounds (4–5)

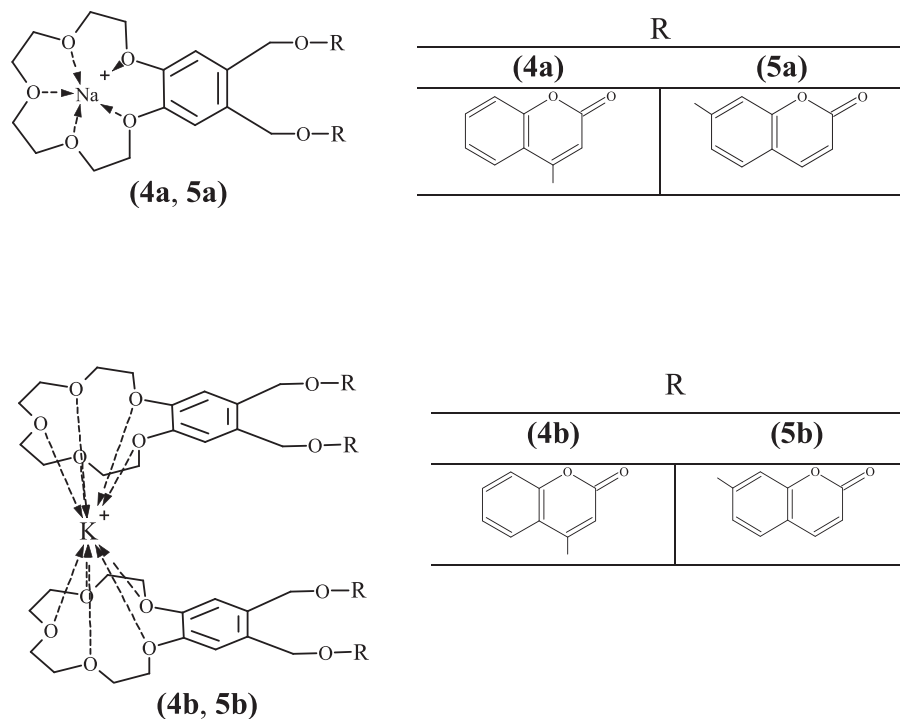
The hydroxycoumarin compounds (4-hydroxycoumarin or 7-hydroxycoumarin) (1.78 g, 11 mmol) was dissolved in 25 mL acetone. Then, KOH solution (0.76 g, 13.60 mmol) was dropwise added and the reaction mixture was stirred for 1 h. To dissolve the resulting salt, 2 mL of distilled water was added to the reaction media. Subsequently, 4',5'-bis(bromomethyl)benzo-15-crown-5 (2.50 g, 5.51 mmol) in 20 mL acetone was slowly added to the reaction mixture. The solution was refluxed for 24 h and the consumption of the starting material was monitored using thin layer chromatography (silica, eluent; chloroform). After the reaction was complete, the solubility differences in THF, acetone and dichloromethane of compound were utilized for the purification of the product. The white precipitate formed was isolated and recrystallized from dichloromethane.

2.2.2. General procedure for the synthesis of chromone compounds (6–11)

The chromone aldehydes (3-formylchromone or 6-methyl-3-formylchromone) (8.8 mmol) were dissolved in 25 mL solvent (MeOH or EtOH or PrOH). 4'-amino-benzo-15-crown-5 (8.8 mmol)



Scheme 2. Synthesis of new coumarin-crown ether compounds (**4** and **5**).

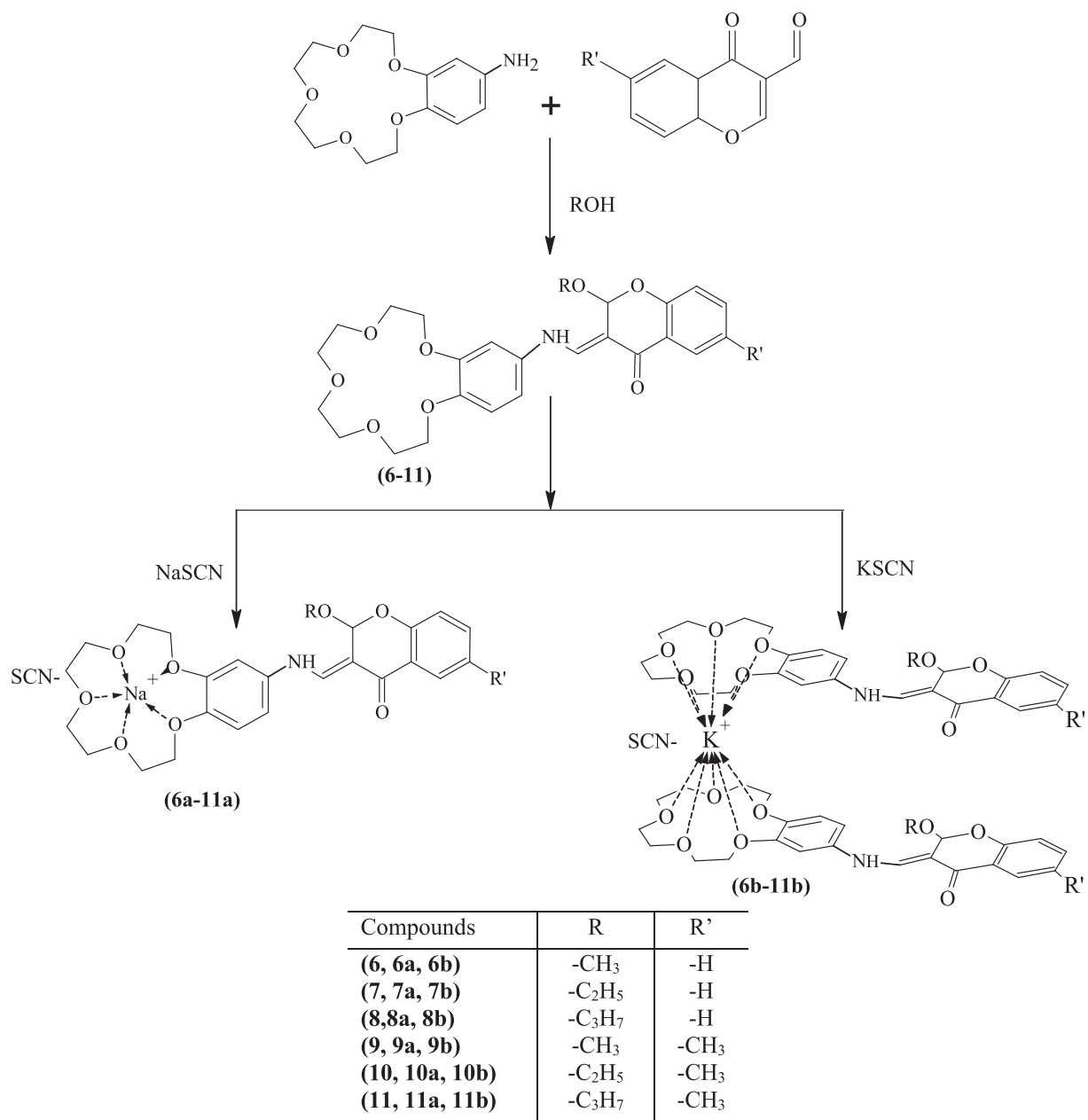


Scheme 3. Synthesis of new coumarin-crown ether sodium and potassium complexes (**4a**, **5a** and **4b**, **5b**).

was dissolved in 25 mL solvent (MeOH or EtOH or PrOH) and added dropwise to the chromone solution. The resulting solution was stirred under reflux 4 h. The crude products were recrystallized from ethanol.

2.2.3. General procedure for the synthesis of sodium complexes (**4a**–**11a**)

The corresponding crown ether (**4**–**11**) (2 mmol) and NaSCN (2 mmol) were dissolved in 10 mL solvent (THF for **4** and **5**, EtOH for **6**–**11**) and heated to reflux for 2 h. The crude sodium complex was



Scheme 4. Synthesis of new chromone-crown ether compounds (**6-11**), sodium and potassium complexes (**6a-11a** and **6b-11b**).

filtered and recrystallized from ethanol.

2.2.4. General procedure for the synthesis of potassium complexes (**4b-11b**)

The corresponding crown ether (**4-11**) (2 mmol) and KSCN (1 mmol) were dissolved in solvent (in THF for **4** and **5**, in EtOH for **6-11**) (10 mL) and heated to reflux for 2 h. The crude potassium complex was filtered and recrystallized from ethanol.

2.3. Antimicrobial evaluation

The antimicrobial activity of crown-coumarin compounds (**4-11**) and alkali metal complexes (**4a, 5a, 4b** and **5b**) were screened selected pathogenic bacteria against; *Listeria monocytogenes* 4b ATCC 19115, *Staphylococcus aureus* ATCC 25923, *Staphylococcus epidermidis* ATCC 12228, *Bacillus cereus* NRLL B-3008, *Micrococcus*

luteus ATCC 93419 as Gram (+) bacteria; *Salmonella typhi* H NCTC 901.8394, *Shigella dysenteriae* type 2 NCTC 2966, *Escherichia coli* ATCC 1280, *Proteus vulgaris* ATCC 6059, *Klebsiella pneumoniae* ATCC 27853, *Serratia marcescens* sp. as Gram (–) bacteria and *Candida albicans* ATCC 90028 as yeast.

Synthesized ligands and complexes were maintained at room temperature and dissolved (10 µM) in DMSO. DMSO was used as a control solvent because, it has no antimicrobial activity against any of the tested microorganisms. Detection of antibacterial and antifungal activity of synthesized compounds and alkali metal complexes were performed using the well-diffusion method. The modified polymers were kept dry at room temperature and were dissolved in DMSO (0.15 g/mL). 1% (v/v) of 24 broth culture containing 10⁶ CFU/mL was placed in sterile petri dishes. Mueller-Hinton Agar (15 mL) was used to culture the test bacteria and it was kept at 45 °C. The molten nutrient agar was added into Petri-

dishes and allowed to solidify. Then, 6 mm diameter holes were punched using a sterile cork borer and were completely filled with the test solutions. The plates were incubated at 37 °C for 24 h. After incubation process, the mean value was obtained for all holes and it was used to calculate the zone of growth inhibition each samples against the pathogenic microorganism. The pathogenic bacteria cultures and yeast were tested for resistance to five standart antibiotics produced by Oxoid Lt., Basingstoke, UK. These were: Ampicillin, Nystatin, Kanamycin, Sulphamethoxazol, Amoxycillin [40–43].

3. Results and discussion

3.1. Syntheses and structural characterization

The coumarin substituted crown ether ligands (**4**, **5**) were successfully synthesized with the yields of 38% and 57%, respectively and the synthesis coumarin derivatives were conducted as outline in Scheme 2.

The reaction products of 3-formylchromone and 6-methyl-3-formylchromone with 4'-amino-benzo-15-crown-5 in different solvent media were investigated. In these reactions, with the opening of the pyrone ring, new chromanone compounds are obtained by the nucleophilic addition mechanism [10]. According to previous studies, nucleophiles can react in three electrophilic sites of 3-formylchromones. The spectral study and calculated results the C-2 atom of the 3-formylchromones is the most strongly activated towards nucleophilic reactions [10,44] (Scheme 1). The 3-formylchromone was expected to react easily with the primary amines in the alcoholic medium to give the Schiff base. However, instead of the imine compound in the alcoholic medium, the enamine compound was obtained [45].

The sodium and potassium complexes (**4a**, **5a** and **4b**, **5b**) were prepared by the reactions of a solution of the ligands in THF (for **4** and **5**) or EtOH (for **6-11**) with NaSCN or KSCN. The spectroscopic data indicated that the stoichiometry of the sodium complexes (**4a**, **5a**) formed between Na⁺:benzo-15-crown-5 was 1:1 (Metal:Ligand) and potassium complexes (**4b**, **5b**) formed between K⁺:benzo-15-crown-5 was 1:2 (Metal:Ligand).

While all ligands (**4-11**) and coumarin-crown ether complexes (**4a**, **5a**, **4b**, **5b**) are stable in solution, the alkali metal complexes (**6a-11a**, **6b-11b**) of chromon-crown ether compounds are partially or completely hydrolyzed in solution. The structures of compounds and complexes have been verified by elemental analysis, FTIR, ¹H, ¹³C NMR and mass spectra. Analytical characterizations and experimental details of the ligands (**4-11**) and complexes (**4a-11a** and **4b-11b**) were given in Table S1.

3.2. Mass spectra

The mass spectra of ligands and complexes were recorded using LC-MS and HRMS TOF-ESI positive ion screening method. The molecular ion peaks and molecular fragments of the new compounds and metal complexes were in good agreement with the proposed structures. In the mass spectra of compounds (**4**, **6**, **7**, **9-11**) dominant peaks were observed at 639.18335 (100%) (Fig. S1), 494.4 (100%) (Fig. S1), 508.1 (100%) (Fig. S1), 508.5 (100%), 522.21245 (22%), 536.22824 (25%), respectively. These peaks corresponding to m/z [M+Na]⁺ (molecular ion plus sodium). For compound **5**, the peak at 617.20275 (83%) corresponding to m/z [M+H]⁺ (molecular ion) was recorded (Fig. S1). In the electrospray (ES) mass spectrum of compound **8**, the molecular ion peak was not observed, but fragments of significant abundance were detected at m/z 494.2 (100%) corresponding to the [M + Na–C₂H₅].

The mass spectra of sodium and potassium complexes were

characterized by intense peak for **4a**, **6a**, **8a** and **6b** m/z [M]⁺ 639.18118 (100%) (Fig. S2), 494.17877 (100%) (Fig. S2), 522.21003 (100%) and 981.34119 (100%) (Fig. S2), respectively. In the mass spectra of complexes (**9a-11a**, **7b**, **9b-11b**), the molecular ion peaks were not detected, but the important fragments of significant abundance were observed.

3.3. FT-IR spectra

The IR spectra of coumarin (**4** and **5**) and chromone (**6-11**) compounds were registered and characteristic IR bands and corresponding assignment are presented in Table S2. In all compounds (**4-11**) and complexes (**4a-11a**, **4b-11b**), the alkyl ether ν (C–O–C)_{aliph.} and aryl ether ν (C–O–C)_{arom.} stretching bands were observed as sharp peaks in the range of 1095–1142 cm^{−1} and 1119–1244 cm^{−1}, respectively. Characteristic peaks of carbonyl group (C=O) of **4** and **5** were appeared to 1720 and 1707 cm^{−1}, respectively.

IR spectral data of enamine compounds formed by the reaction of chromone and primary amines are available in the literature [10,18,37,38]. In these compounds, the strong bands at 1654, 1646, 1649, 1651, 1645, 1645 cm^{−1} in spectra of **6-11**, respectively were similar and they were assigned as ν (C=O) in chromanones. The disappearance of ν (C=O) bands of the aldehyde group in **6-11**, confirms their condensation with molecules of crown-amine. Another characteristic peak for chromone substituted compounds were N–H stretching and these peaks for **6-11** were 1590, 1591, 1589, 1608, 1589 and 1589 cm^{−1}, respectively.

IR spectra of the sodium and potassium complexes (**4a-11a** **4b-11b**) showed the ligands band with the appropriate shifts due to complex formation (Table S3). The presence of thiocyanate for complex (**4a-11a** **4b-11b**) was indicated by the characteristic broad band at 2058, 2059, 2054, 2056, 2058, 2058, 2068, 2052, 2059, 2062, 2044, 2046, 2048, 2050, 2052 and 2050 cm^{−1}. When the IR spectra of the chromanone ligands and alkali metal complexes were evaluated, it was observed that the ligands preserved the enamine structure in complex formation.

3.4. ¹H and ¹³C NMR spectroscopy

In order to identify structures of coumarine and chromone substituted benzo-15-crown-5 compounds (**4-11**) and alkali metal complexes (**4a-11a**, **4b-11b**) ¹H NMR spectra were recorded in CDCl₃ and DMSO (Table S4 and Table S5).

For the coumarin-crown ether compounds (**4** and **5**) spectra (Fig. S3 for compound **5**) indicate that the molecules are symmetric. The crown ether proton (–OCH₂–CH₂O–) peaks for **4** and **5** were seen to resonate between at δ 3.74–4.17 and 3.29–4.06 ppm, respectively. The –CH₂– protons were observed as a singlet at δ 5.47 and 5.21 ppm for the compounds **4** and **5**.

In proton NMR, chromone-crown ethers (**6-11**) (Fig. S3 for compound **8**) display two doublet peaks at the region of δ 7.36–7.97 and 12.14–12.72 ppm. A doublet at the region of the δ 7.36–7.97 ppm indicated the presence of –CH proton. Another doublet at δ 12.14–12.71 ppm was assign to NH proton. The relatively high downfield shift for NH proton is due to the strong intramolecular hydrogen bond [46]. ¹H NMR spectra of the chromanones (**6-11**) showed a singlet signal of CH of the pyrone ring at δ 5.64–5.78 ppm.

The ¹H NMR spectra of the sodium and potassium complexes (**4a**, **5a**, **4b**, **5b**) (Fig. S4 for compounds **5a** and **4b**) were approximately the same as in the corresponding ligand spectra. The complexing of the ligands with Na⁺ cations is called “filling complexes” while the complexes formed by the K⁺ cation which is greater than the benzo-15-crown-5 cavity are called “sandwich complexes”

[47,48]. The ^1H NMR spectral data provide important evidence for the ligands and metal complexes [49]. Because different multiplet peaks were detected in crown ether protons region for sodium and potassium complexes [40]. Although three multiplet peaks observed for the ligands (**4** and **5**), four multiplet peaks were seen for the sodium complexes (**4a**, **5a**) and a broad peaks were seen for the potassium complexes in crown ether proton peaks region [48,50,51].

When sodium and potassium complexes of chromone-crown ether compounds (**6a-11a**, **6b-11b**) were examined, similar changes were observed with coumarin compounds in crown ether proton peaks region. However, NH, CH–NH and CH peaks were not seen in chromone-crown ether complexes (**6a-11a** and **6b-11b**). New single peaks were observed in all complexes in the range of δ 8.51–8.55 and δ 10.37–10.40 ppm (Fig. 1).

These peaks were determined to belong to the 3-formylchromone and 6-methyl-3-formylchromone used as starting material. This was proof that the complexes are hydrolyzed in solution. The complexes were stable in solid form, but unstable in solution. Because, the elemental analysis and the IR spectra confirmed that the complexes were stable in solid form (Table S2 and Table S3).

The ^{13}C NMR spectral data and numbering of carbon atoms are given in Table S6 and Table S7. The coumarine compounds (**4**, **5**) and alkali metal complexes (**4a**, **5a**, **4b** and **5b**) spectra indicate that the molecules are symmetric. The characteristic signals of the four crown ether carbons for **4**, **5**, **5a**, **5b** were observed between 68.31 and 71.39 ppm. The carbonyl carbons for compounds **4**, **5**, **5a** and **5b** were observed at 163.97, 161.54, 161.83 and 161.76 ppm, respectively. In all of the chromanone ligands (**6-11**), the characteristic carbonyl (C=O) carbons were detected at 180.73, 181.16, 180.97, 180.92, 181.06, 181.16 ppm, respectively. The carbon atom of C=NH group for **6-11** was observed at 144.86–144.51 ppm. While chromon-crown ether alkali metal complexes (**6a-11a** and **6b-11b**) are stable in solid state, they are readily hydrolyzed in solution. In this respect, ^{13}C NMR spectra were also observed to be quite mixed.

3.5. Antimicrobial activity

The compounds and their metal complexes were screened for antimicrobial activity DMSO solvent as a control substance. The compounds and complexes were tested with the same

concentrations in DMSO solutions (0,1 $\mu\text{g}/\mu\text{L}$). **4-11**, **4a**, **5a**, **4b** and **5b** were screened for their antimicrobial activities against selected pathogenic microorganisms by the well-diffusion method.

All synthesized compounds exhibited varying degrees of inhibitory effects on the growth of different tested strains (Fig. 2). All of the compounds and complexes were effective *B.cereus*, *M.luteus* and *Proteus vulgaris*. *B.cereus* is known as opportunist pathogens and is associated with food-borne illness [52]. *M. luteus* has considered an opportunistic pathogen that can be responsible for nosocomial infections. Furthermore can cause skin infections and septic shock in immunocompromised peoples. In addition to all this, *P. vulgaris* has been isolated from a patients in long-term care facilities and hospitals, and from patients with underlying diseases or with weak immune systems. Patients with recurrent infection, those with structural abnormalities in urinary tract, those with urethral instrumentation and those with hospital infection, *Proteus* spp. and other microorganisms.

All compounds and complexes showed moderate activity against *Serratia marcescens*, except for compound **10**. Ligands and complexes were completely inactive against *Shigella dysenteria*, except for compound **5** (15 mm). All chromone compounds (**6-11**) showed moderate activity against *L. monocytogenes* (20 mm, 17 mm, 20 mm, 18 mm, 16 mm and 17 mm, respectively). The pathogen is the causative agent of listeriosis which is the leading cause of death among foodborne bacterial pathogens [53].

S. epidermis which infections were associated with intravascular devices (prosthetic heart valves, etc.), furthermore generally happen in prosthetic joints, catheters and large wounds. *S.epidermis* gain resistance against traditional antibiotics every day and there was need for more effective antibiotics for the treatment of disease [54,55]. The compound **10** showed most activity against *S. epidermis* (23 mm).

Compounds and complexes had moderate activity for *E. coli*, except for compound **7**.

Salmonella serovars cause very diverse clinical symptoms, from asymptomatic infection to serious typhoid-like syndromes in infants or certain highly susceptible animals [42,56,57]. It was determined that many of the synthesized compounds and complexes (**4**, **7**, **8**, **9**, **11**, **4a**, **4b**, **5a**, **5b**) showed activity against *S. typhi* H.

The sodium and potassium complexes (**4a**, **5a**, **4b**, **5b**) of coumarin compounds showed a significant activity against *Klebsiella pneumonia*; however **4** and **5** did not showed any activity

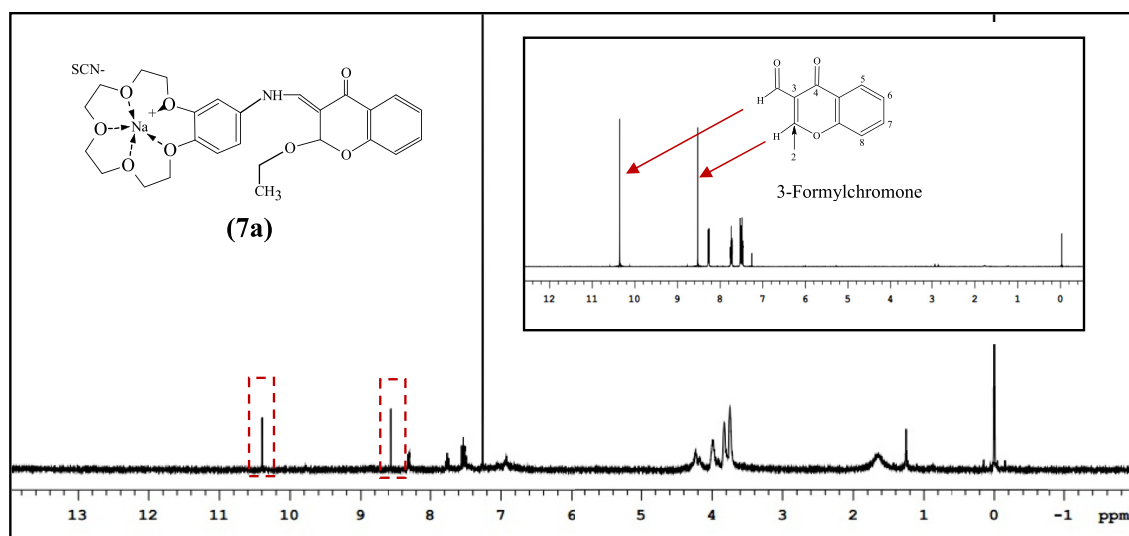


Fig. 1. ^1H NMR spectra of sodium complex (**7a**) and 3-formylchromone.

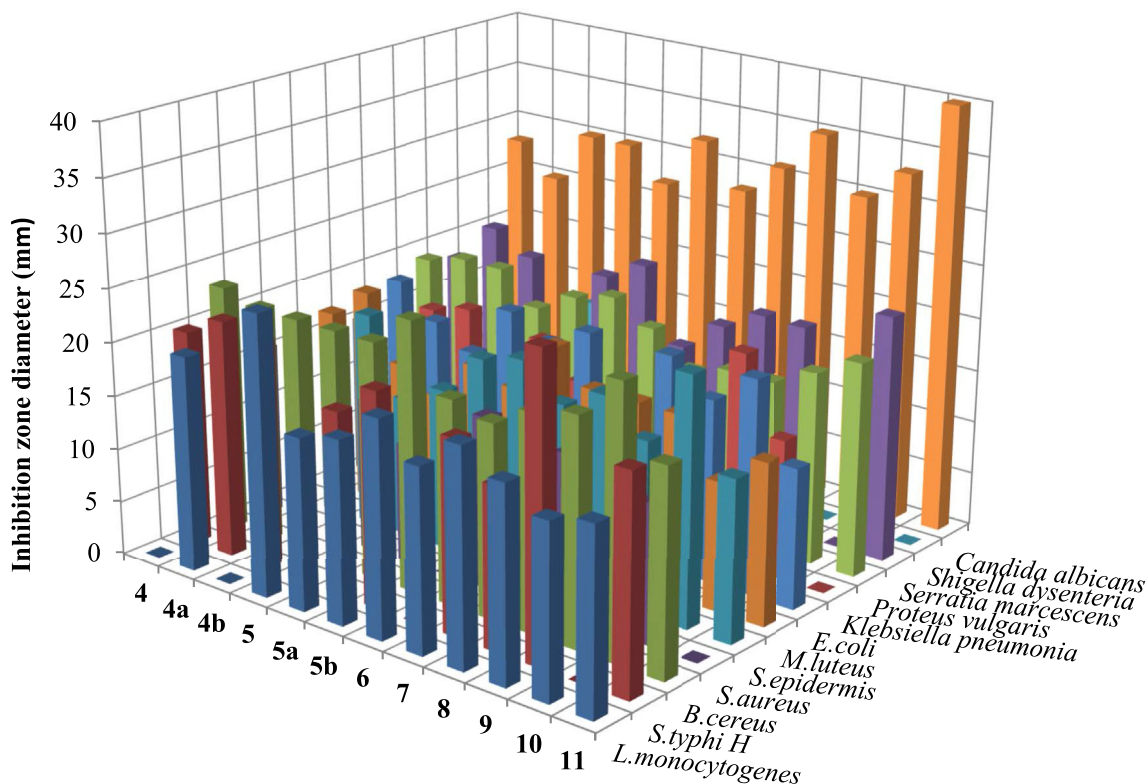


Fig. 2. Antimicrobial activity of ligands (4–11) and complexes (4a, 4b, 5a and 5b) (diameter of zone inhibition (mm)).

against this bacteria. The potassium complexes (4b, 5b) were not effective against *S. aureus*.

Systemic fungal infections, including those by *Candida albicans* have emerged as important causes of morbidity and mortality in immune compromised patient (Aids, cancer chemotherapy, organ or bond transplantation) [56]. All synthesized ligands and complexes showed best antimicrobial activity against *Candida albicans* (Fig. S5). For coumarin compounds and alkali metal complexes, the potassium complexes (4b, 5b) were more effective than ligands (4, 5) and sodium complexes (4a, 5a). The chromone compounds (6–11) showed good activity against *Candida albicans*. Three electron-donor derivatives were prepared, containing methoxy, ethoxy and propoxy. The antifungal test revealed that their activity order was propoxy > ethoxy > methoxy for *Candida albicans*. Chromones with the electron releasing groups the antifungal activity increased while as the aryl proton is replaced with electron-withdrawing group the antifungal activity decreased [58–61].

The antibacterial activity of these compounds was compared with seven commercial antibiotics: Ampicillin, Nystatin, Kanamycin, Sulphamethoxazol and Amoxycillin (Fig. S6). The synthesized compounds were as effective as the antibiotics mentioned. However, the all compounds and complexes had a greater effect on yeast than antibiotics.

3.6. Photophysical study

The chemosensing properties of 4–11 were further investigated by UV–Vis. and fluorescence spectroscopy. The recognition behaviours of 4–11 towards various metal ions were investigated. The absorption and emission spectra were recorded in a series of additional metal nitrate concentrations in THF: EtOH (1:1, v/v) for coumarin-crown ether compounds (4 and 5) and in EtOH for chromone-crown ether compounds (6–11). In the absorption

spectra of compounds 4–11, no significant change were observed for all other cations except Fe^{3+} and Cu^{2+} .

The absorption spectra of compounds 4 and 5 reveal one band at 305 and 320 nm, respectively. The addition of Fe^{3+} and Cu^{2+} metal ions led to the great increase of the original absorbance (Fig. 3). Such absorbance change may be ascribed to the newly formed complex and the absorption of Fe^{3+} and Cu^{2+} in the UV–Vis region [62].

To determine the selectivity range of compounds 4 and 5 toward Fe^{3+} and Cu^{2+} metal ions, the titration experiment was conducted (Figs. 4 and 5 for compound 4, Fig. S7 and Fig. S8 for compound 5). Absorption of compounds (4 and 5) at 305 and 320 nm (molar extinction coefficient $\epsilon = 8120 \text{ M}^{-1}\text{cm}^{-1}$ and $\epsilon = 13680 \text{ M}^{-1}\text{cm}^{-1}$) increased with increasing Fe^{3+} and Cu^{2+} concentration.

Compounds 4 and 5 exhibited strong fluorescence emission at 387 nm in THF:EtOH (1:1, v/v) ($\Phi_{\text{fr}} = 0,098$ and $\Phi_{\text{fr}} = 0,153$, respectively), (Rhodamine in THF:EtOH (1:1, v/v) was used as the reference compound). Upon addition of Fe^{3+} and Cu^{2+} , the fluorescence of 4 and 5 was significantly quenched with the increase of metal ion concentrations. When fluorescence compounds are coordinated with metal ions, they do not show a shift in the emission spectra but they show significant quenching or enhancement [63]. The quenched emission intensity is probably due to the complex of Fe^{3+} and Cu^{2+} with compounds (4 and 5). Paramagnetic metal ions such as Cu (II) and Fe (III) generally show fluorescence quenching [4,64–66]. The quenching behaviour of Fe^{3+} and Cu^{2+} for 4 and 5 might be attributed to the reverse PET mechanism involving electron donating from the excited coumarin unit to the crown ether unit. Thus, the coumarin group behave as an excited electron donor and the crown ether group behave as an electron acceptor. The reverse-PET sensor are fluorescent in the absence of metal cation and cation binding induces an electron transfer from the fluorophore to the receptor [57].

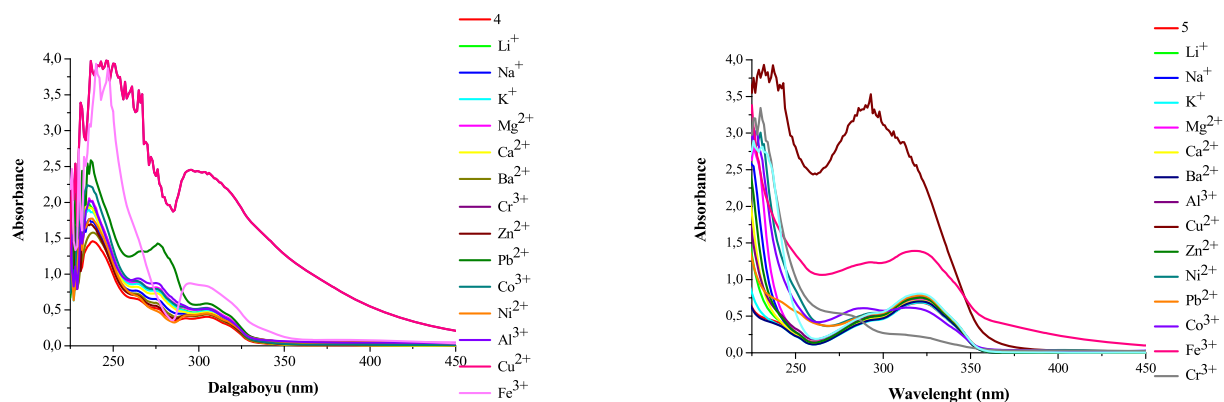


Fig. 3. Absorption spectra of coumarin-crown ether (**4** and **5**) (5×10^{-5} M), in the presence of the metal salts ($M(\text{NO}_3)_n$) (100 eq) in THF:EtOH (1:1, v/v).

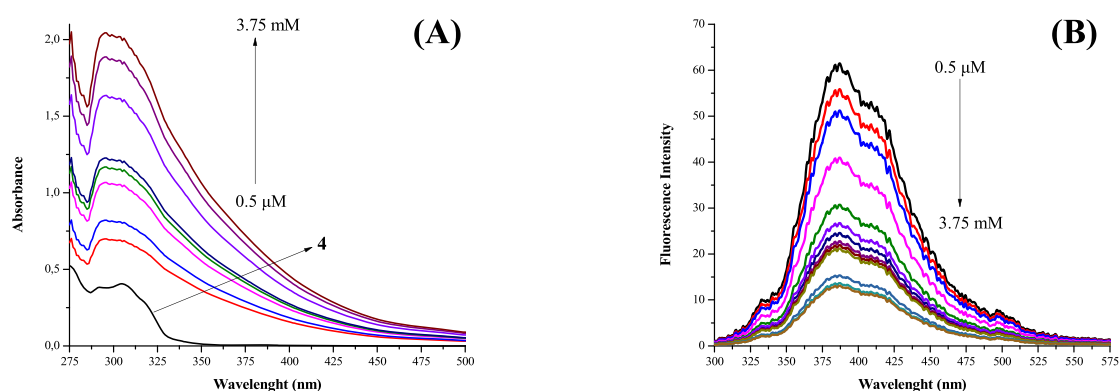


Fig. 4. (A) Changes of absorption analysis of compound **4** in different Fe^{3+} concentrations (0.5 μM –3.75 mM) (B) emission spectra of compound **4** on increasing addition of Fe^{3+} solution (0.5 μM –3.75 mM) in THF:EtOH (1:1) ($\lambda_{\text{ex}} = 251$ nm).

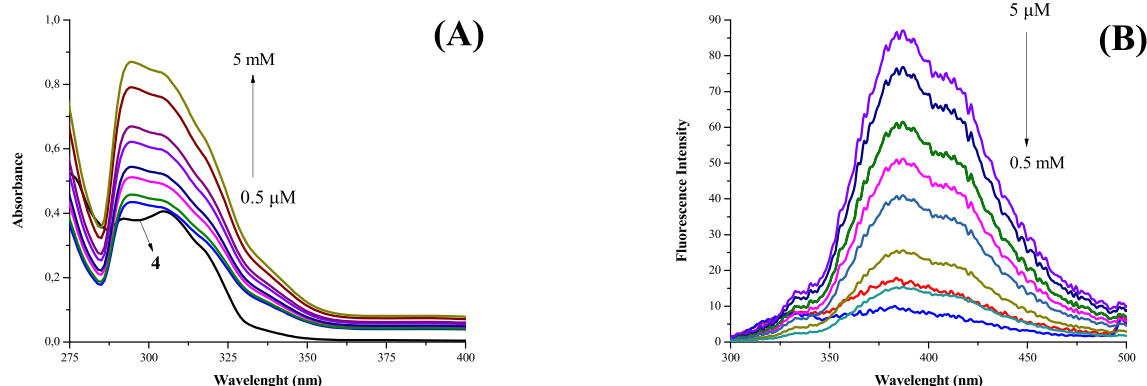


Fig. 5. (A) Changes of absorption analysis of compound **4** in different Cu^{2+} concentrations (0.5 μM –5 mM) (B) emission spectra of compound **4** on increasing addition of Cu^{2+} solution (0.5 μM –5 mM) in THF:EtOH (1:1) ($\lambda_{\text{ex}} = 251$ nm).

UV–visible spectroscopic measurements of chromone-crown ether compounds (**6–11**) were detected in EtOH at ambient temperature. All chromone-crown ether ligands (**6–11**) showed an absorption band at 397 nm ($\epsilon = 18060 \text{ M}^{-1}\text{cm}^{-1}$, $\epsilon = 19020 \text{ M}^{-1}\text{cm}^{-1}$, $\epsilon = 18060 \text{ M}^{-1}\text{cm}^{-1}$, $\epsilon = 29060 \text{ M}^{-1}\text{cm}^{-1}$, $\epsilon = 5560 \text{ M}^{-1}\text{cm}^{-1}$, $\epsilon = 15880 \text{ M}^{-1}\text{cm}^{-1}$, $\epsilon = 16100 \text{ M}^{-1}\text{cm}^{-1}$, respectively). This peak is due to the newly formed aminomethylene group and belongs to the $n\text{-}\pi^*$ transition [68]. The addition of metal ions led to the great increase and strongly hypsochromic-shift ($\Delta\lambda = 97$ nm for Fe^{3+} ,

$\Delta\lambda = 72$ nm for Cu^{2+}) of the absorbance band (Fig. 6).

The titration experiments were performed to determine the selectivity range of Fe^{3+} and Cu^{2+} metal ions of compounds **6–11** (Figs. 7 and 8 for compound **9**, Figs. S9–S19 for compounds **6**, **7**, **8**, **10** and **11**). When Fe^{3+} and Cu^{2+} ions were added to the solutions of **6–11**, the absorption band at 397 nm decreased and new bands appeared. These new bands are caused by Fe^{3+} and Cu^{2+} complexes. Compounds (**6–11**) exhibited weak fluorescence at the range of 360–376 nm in EtOH upon excitation at around 300 nm

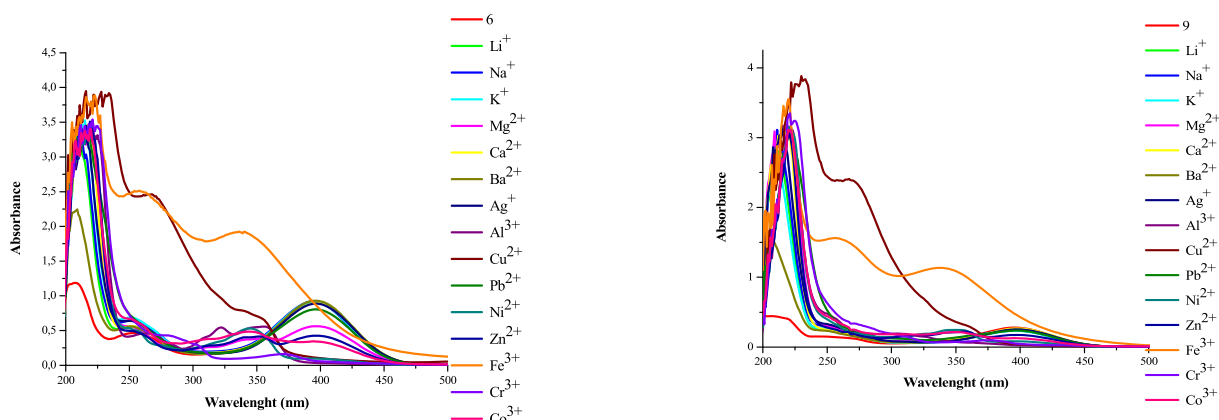


Fig. 6. Absorption spectra of chromone-crown ether compounds (**6** and **9**) (5×10^{-5} M), in the presence of the metal salts ($M(\text{NO}_3)_n$) (100 eq) in EtOH.

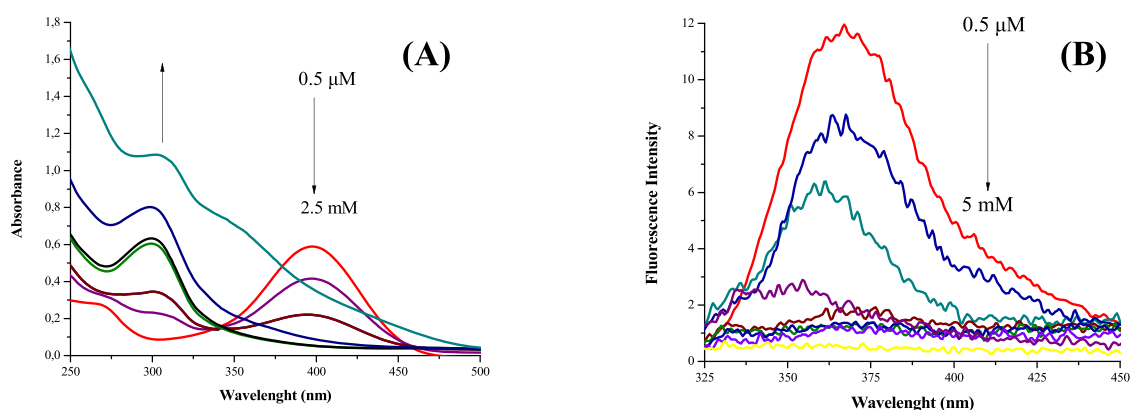


Fig. 7. (A) Changes of absorption (0.5 μM -2.5 mM) in the different Fe^{3+} concentrations (B) emission $\lambda_{\text{ex}} = 300$ nm spectra of compound **9** (5×10^{-5} M) on increasing addition of $\text{Fe}(\text{NO}_3)_3$ solution (0.5 μM -5 mM) in EtOH.

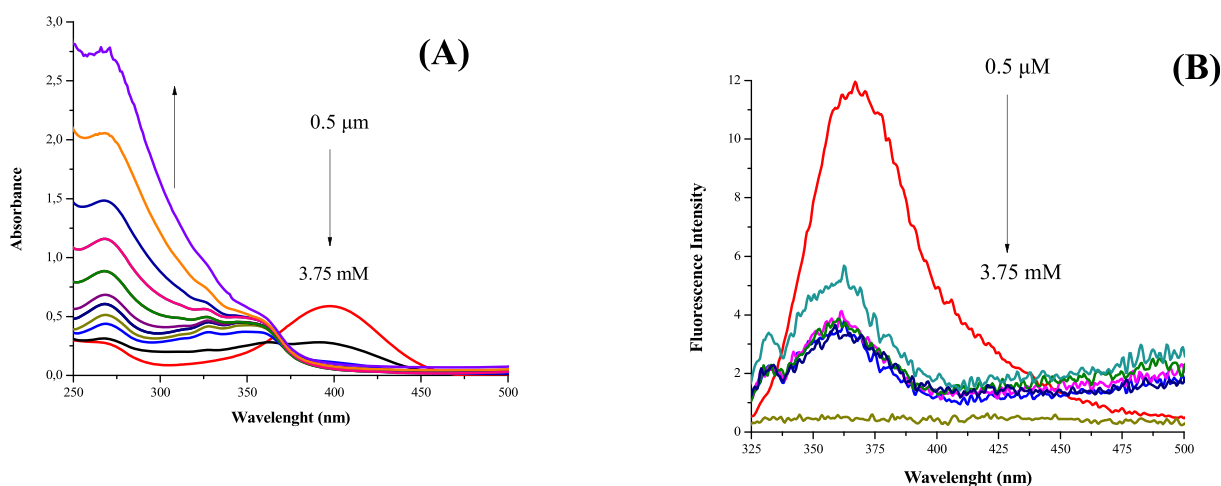


Fig. 8. (A) Changes of absorption (0.5 μM -3.75 mM) in the different Cu^{2+} concentrations (B) emission $\lambda_{\text{ex}} = 300$ nm spectra of compound **9** (5×10^{-5} M) on increasing addition of $\text{Cu}(\text{NO}_3)_2$ solution (0.5 μM -3.75 mM) in EtOH.

($\Phi_{\text{fr}} = 0,1426$, $\Phi_{\text{fr}} = 0,0891$, $\Phi_{\text{fr}} = 0,1608$, $\Phi_{\text{fr}} = 0,0946$, $\Phi_{\text{fr}} = 0,9493$, $\Phi_{\text{fr}} = 0,0417$, respectively, (Rhodamine in ethanol was used as reference compound). The fluorescence of compounds **6-11** was significantly quenched by the increase in metal ion (Fe^{3+} and Cu^{2+}) concentrations and slightly shifted to blue. Coordination between Fe^{3+} or Cu^{2+} and ligands may reduce the electron-donating ability

of the chromone group to the crown ether ring. This causes blue shift in the spectrum, and the absorption density increases with increasing Fe^{3+} and Cu^{2+} concentration. ICT sensors consist entirely of conjugated π -systems and have an integrated receptor and fluorophore, in contrast to PET sensors with an electron donor part separated by a spacer from the fluorophore [4]. Interaction with the

donating group, it should be noted that only a slight blue shift of the absorption and emission spectra is observed in these cases [67,69,70].

Binding constants were determined from titration studies of Fe^{3+} and Cu^{2+} metal ions of compounds **4-11**. The stability constants of ionophore-metal ion complexes determined from the Benesi-Hildebrand plot are shown in Fig. 9. These values calculated from absorbance measurement are in agreement with binding constant reported in literature [71–74]. The highest values for all compounds (**4-11**) was obtained with Fe^{3+} in THF:EtOH (1:1, v/v) and EtOH. These results show that compounds are more selective to Fe^{3+} metal ion.

4. Conclusions

In this study, coumarine and chromone substituted new benzo-15-crown-5 ligands (**4-11**) and alkali metal (Na^+ , K^+) complexes (**4a-11a**, **4b-11b**) were synthesized and characterized by using analytical and spectral techniques. Coumarine compounds (**4** and **5**) were prepared by the reaction of 4',5'-bis(bromomethyl)-benzo-15-crown-5 and hydroxycoumarine derivatives in basic media. Two different series of chromone substituted crown ethers (**6-8** and **9-11**) were synthesized by the condensation reactions of 4-amino-benzo-15-crown-5 with 3-formylchromone and 6-methyl-3-formylchromone in different solvent media. The chemosensing behaviours of **4-11** was carried out using UV–Vis and fluorescence spectroscopy. Absorption intensity of coumarine compounds (**4** and **5**) increased with the addition of Fe^{3+} and Cu^{2+} , but fluorescence was quenched. While a sharp blue shift was observed in the absorption spectrum of chromone compounds (**6-11**), a slight blue shift and fluorescence quenching were observed in the fluorescence spectrum. The results indicates that chemosensors **4-11** could be used as a Fe^{3+} and Cu^{2+} selective fluorescent in the presence of other competing ions. The synthesized compounds (**4-11**, **4a**, **5a**, **4b**, **5b**) have been found to exhibit antibacterial and antifungal activities at moderate to good levels both gram negative and gram positive bacteria. The antimicrobial activity of these compounds was also compared with commercial (standard) antibiotics. It was seen that the synthesized compounds were effective as the antibiotics and antifungal mentioned. Synthesized compounds and complexes (**4-11**, **4a**, **5a**, **4b**, **5b**) have been found to be more effective than antibiotics and antifungal (*C. albicans*; all compounds, 25–40 mm). As a result, synthesized compounds may become potential candidates for the clinical trials.

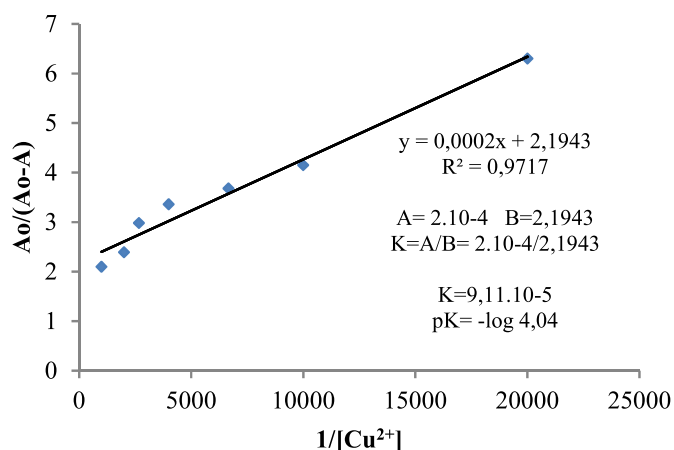


Fig. 9. Linear regression curve for compound **7** and stability constant of metal ion complexes of **4-11**.

Author contributions section

Zeliha Hayvalı; designed the study and conceived and planned the experiments. Duygu Şahin Gül; carried out the experiments and analysed spectra. Hatice Ogutcu; did antimicrobial studies of new compounds. Zeliha Hayvalı wrote the manuscript with support from Duygu Şahin Gül and Hatice Ogutcu. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.molstruc.2019.127569>.

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