

## Synthesis and antimicrobial activity of new crown ethers of Schiff base type

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**Abstract:** New crown ether ligands of the Schiff base type (**4a–d**) were synthesized by the reaction of 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde and 2-hydroxy-1-naphthaldehyde with 6,7-dihydro-13*H*-dibenzo[*e,h*] [1,4]dioxonin-2,11-diamine (**3**). The structures of ligands were investigated by elemental analysis as well as IR, UV–visible, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and MS spectroscopic data. The antimicrobial and anti-yeast activities of the ligands were screened *in vitro* against the organisms *Escherichia coli* ATCC 11230, *Staphylococcus aureus* ATCC 6538, *Klebsiella pneumoniae* UC57, *Micrococcus luteus* La 2971, *Proteus vulgaris* ATCC 8427, *Pseudomonas aeruginosa* ATCC 27853, *Mycobacterium smegmatis* CCM 2067, *Bacillus cereus* ATCC 7064, *Listeria monocytogenes* ATCC 15313, *Candida albicans* ATCC 10231, *Kluyveromyces fragilis* NRRL 2415, *Rhodotorula rubra* DSM 70403, *Debaryomyces hansenii* DSM 70238 and *Hanseniaspora guilliermondii* DSM 3432.

**Keywords:** crown ether, Schiff base, antimicrobial activity, spectroscopy.

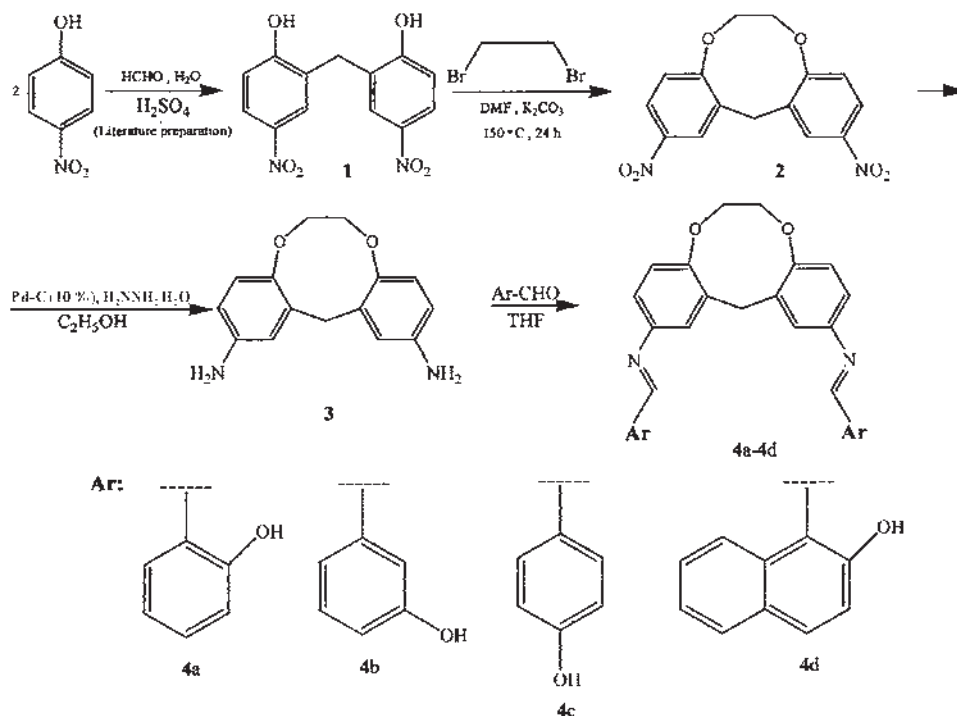
### INTRODUCTION

The study of macrocyclic ethers has attracted great interest in the last decades, not only from the synthetic and selective alkali and alkaline earth cation complexation properties point of view, but also with respect to their unusual characteristics.<sup>1,2</sup> For the linkage of two crown ether units by means of aliphatic or aromatic chains, ester,<sup>3–5</sup> amide,<sup>6,7</sup> calixarene<sup>8–17</sup> and Schiff base type<sup>18–20</sup> precursors are commonly used. Macrocyclic polyethers form complexes with alkali metals, alkaline earth metals, and with some other metal ions, with oxonium ions, with protonated amines, including amino acids, and also with some neutral molecules such as acetonitrile. In addition to homonuclear mono- and ditopic complexes of bis(crown ethers) with alkali and alkaline earth metal ions, heteroatoms of the linkage unit be-

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tween the two crown ether rings can form complexes with transition metal cations<sup>21</sup> to yield interesting heteronuclear oligotopic complexes of bis(crown ethers) in solution and in the solid state.<sup>1</sup> Complexes of this type may be used as simple models for biological systems, such as metalloenzymes.<sup>22</sup>

In this study, new macrocyclic polyether ligands of the Schiff base type were synthesized by the reaction of diamino crown ether **3** with 2-, 3- and 4-hydroxybenzaldehyde and 2-hydroxy-1-naphthaldehyde (Scheme 1).<sup>23</sup> The structures of the synthesized Schiff bases were established by elemental analysis as well as IR, UV-visible, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR and MS spectroscopy. The ligands were screened *in vitro* against microorganisms by the disc diffusion method.<sup>24,25</sup>



Scheme 1.

## RESULTS AND DISCUSSION

In the present study, dinitro-crown ether **2** was synthesized by the reaction of 2,2'-methylenebis[4-nitrophenol] (**1**) with 1,2-dibromoethane. Diamino crown ether **3** was synthesized by the reduction of the corresponding intermediate product, 2,11-dinitro-6,7-dihydro-13*H*-dibenzo[*e,h*][1,4]dioxonin (**2**), with Pd-C (10 %) / hydrazine hydrate in ethanol. The new crown ether ligands of the Schiff base type (**4a-d**) were synthesized by the reaction of diamino crown ether **3** with two equivalents of aromatic aldehyde. The structures of the synthesized Schiff bases were established by elemental analysis as well as IR, MS, UV-visible, <sup>1</sup>H-NMR and

$^{13}\text{C}$ -NMR spectroscopy. The ligands were screened *in vitro* against microorganisms by the disc diffusion method.

The infrared spectra of compounds **4a**, **4b**, **4c** and **4d** show bands at 3448, 3393, 3364 and 3402  $\text{cm}^{-1}$ , respectively, for  $\nu(\text{O-H})$ , 1619, 1624, 1605 and 1623  $\text{cm}^{-1}$ , respectively, for  $\nu(\text{C=N})$ , indicating the formation of Schiff bases (**4a-d**). The aryl and alkyl C-H stretching frequencies of compounds **4a-d** were observed at 3066, 3060, 3070 and 3050  $\text{cm}^{-1}$  and 2933-2878, 2937-2873, 2928-2870 and 2927  $\text{cm}^{-1}$  and  $\nu(\text{C-O-C})$  bands are observed at 1249-1188-1151, 1243-1172-1068, 1239-1162-1167 and 1248-1176-1087  $\text{cm}^{-1}$ , respectively. The  $\nu(\text{C-O})$  vibrations appear at 1364, 1376, 1379 and 1320  $\text{cm}^{-1}$ , respectively, in these ligands (**4a**, **4b**, **4c** and **4d**). The compounds **4a**, **4b** and **4c** with a strong band at 1282, 1287 and 1284  $\text{cm}^{-1}$ , respectively, possess the highest percentage of enol-imino tautomer, due to the stabilization of the phenolic C-O bond.<sup>26</sup>

The UV-visible spectra of compounds **4a-d** were studied in polar (DMSO, ethanol and chloroform) and non-polar (benzene) solvents. The Schiff bases show absorption in the range above 400 nm in polar and non-polar solvents. It should be pointed out that the new band belongs to the keto-amine form of the Schiff bases with the OH group in the ortho position to the imino group in polar and nonpolar solvents in both acidic and basic media.<sup>27-32</sup> The compounds **4a-c** do not show any absorption in the range  $>400$  nm in DMSO, ethanol, chloroform and benzene. For compound **4d**, a new band is observed at  $>400$  nm in the same solvents. Only the phenol-imine tautomer is dominant in DMSO, ethanol, chloroform and benzene for **4a-c**. On the other hand, compound **4d** is in tautomeric equilibria (phenol-imine,  $\text{O-H}\cdots\text{N} \rightleftharpoons \text{keto-amine}$ ,  $\text{O}\cdots\text{H-N}$  forms) in DMSO, eth-

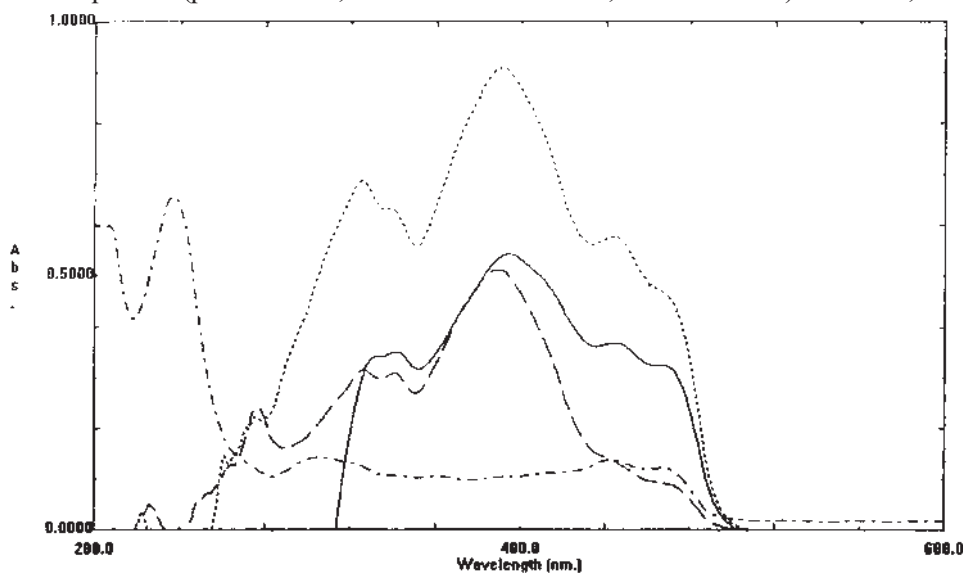


Fig. 1. Solvent effect on compound **4d**. DMSO (—), ethanol (---)  $\text{CHCl}_3$  (.....), benzene (- - -).

anol, chloroform and benzene (Fig. 1). This tautomer is observed in DMSO for **4d** as supported by the UV–visible data, while it is not observed in DMSO by  $^1\text{H-NMR}$  spectroscopy. The calculated percentage of keto-amine form is given in Table I.

TABLE I. The UV-Vis spectra of the compounds **4a–d**

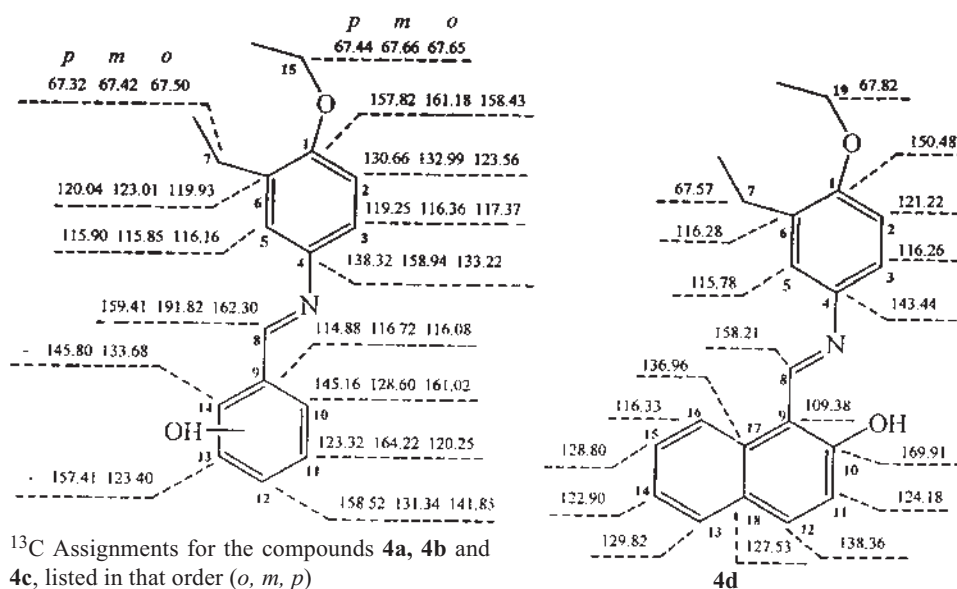
Solvent	Keto-amine tautomer/%			
	<b>4a</b>	<b>4b</b>	<b>4c</b>	<b>4d</b>
DMSO	–	–	–	47
EtOH	–	–	–	43
$\text{CHCl}_3$	–	–	–	33
Benzene	–	–	–	18

The  $^1\text{H-NMR}$  spectra of the compounds **4a–d** show that the tautomeric equilibrium favors the phenol-imine in DMSO. The OH protons are observed as signals at 13.27, 10.78, 10.06 and 15.95 ppm for ligands **4a**, **4b**, **4c** and **4d**, respectively. The azomethine protons are observed as singlets at 8.96, 8.48, 8.55 and 9.69 ppm for **4a–d**, respectively. The phenyl protons are observed as multiplet at  $\delta = 6.51\text{--}8.51$  ppm for compounds **4a–d**. The proton of the etheric group  $\text{Ar-OCH}_2$  also gave a triplet at  $\delta = 4.24$  and 4.31 ppm for **4b** and **4d**, respectively, and a singlet at  $\delta = 4.38$  and 4.34 for **4a** and **4c**, respectively, and  $\text{Ar-CH}_2\text{-Ar}$  gave a singlet at  $\delta = 4.18, 4.15, 4.20$  and 4.08 ppm for **4a–d**, respectively.

The proton de-coupled  $^{13}\text{C-NMR}$  spectra of **4a–d** were analyzed (Scheme 2), and it was concluded that the structures in solution are symmetrical. According to the  $^{13}\text{C-NMR}$  spectra, compounds **4a**, **4b**, **4c** and **4d** have 15, 15, 13 and 19 signals, respectively.

The electron impact MS spectrum of compounds **4a**, **4b**, **4c** and **4d** showed a well-defined parent ion at  $m/z$  464, 464, 464, and 564 (28, 20, 18 and 25 %) with the expected isotope pattern. The peaks at  $m/z$  values of 334, 230, 213 and 108 correspond to the loss of  $(\text{CHC}_6\text{H}_4\text{OH} + \text{CH}_2\text{CH}_2)$ ,  $(\text{CHC}_6\text{H}_4\text{OH} + \text{CH}_2\text{CH}_2 + \text{CHC}_6\text{H}_4\text{OH})$ ,  $(\text{CHC}_6\text{H}_4\text{OH} + \text{CH}_2\text{CH}_2 + \text{CHC}_6\text{H}_4\text{OH} + \text{CH}_2)$ , and  $(\text{CHC}_6\text{H}_4\text{OH} + \text{CH}_2\text{CH}_2\text{OC}_6\text{H}_3\text{CH}_2\text{N-CHC}_6\text{H}_4\text{OH})$  groups for **4a**. The fragmentation patterns of **4b** and **4c** were similar to that of **4a**. The peaks at  $m/z$  values of 360, 334, 212, 120 and 108 correspond to the loss of  $(\text{CHC}_{10}\text{H}_6\text{OH} + \text{CH}_2\text{O})$ ,  $(\text{CHC}_{10}\text{H}_6\text{OH} + \text{OCH}_2\text{CH}_2\text{O})$ ,  $(\text{CHC}_{10}\text{H}_6\text{OH} + \text{CH}_2 + \text{CHC}_{10}\text{H}_6\text{OH})$ ,  $(\text{CH}_2\text{OC}_6\text{H}_3\text{CH}_2\text{N-CHC}_{10}\text{H}_6\text{OH})$  and  $(\text{CHC}_{10}\text{H}_6\text{OH} + \text{CH}_2\text{CH}_2\text{OC}_6\text{H}_3\text{CH}_2\text{N-CHC}_{10}\text{H}_6\text{OH})$  for **4d**. The  $\text{OC}_6\text{H}_4\text{NH}_2$  system in the compounds is stable (dominant ion:  $m/z$  108) during the fragmentation, which indicates first the loss of aldehyde and ethylene fragments.

The antimicrobial activities of the compounds are shown in Table II, in which the inhibition zones formed by standard antibiotic discs are also indicated. As can be clearly seen from Table II, the compounds showed antibacterial activity against both Gram-positive and Gram-negative bacteria and the yeast cultures. In classifying antibacterial activity as Gram-positive or Gram-negative, it would generally be



Scheme 2.

expected that a much greater number would be active against Gram-positive than against Gram-negative bacteria.<sup>33</sup> However, in this study, the compounds were active against both Gram-positive and Gram-negative bacteria and the yeast cultures. Notably, the compounds have stronger antimicrobial activities against the yeast cultures than against bacteria used in this study.

When the obtained results are compared to those of the standard antibiotics, it can be seen that compound **4d** is the most effective compound against bacteria. The compounds have no antibacterial effect against the acid-resistant bacterium *Mycobacterium smegmatis* and *Listeria monocytogenes*. *Staphylococcus aureus* is more susceptible to the compound, as compared to the standard antibiotics except for OFX5 and TE30. Notably, compound **4d** has stronger antibacterial effects than those of the others. Against *Bacillus cereus*, only the compound **4d** has antibacterial activity but its effect is equivalent to the standard SAM20. The compounds have weaker antibacterial activity against *Escherichia coli* and *Klebsiella pneumoniae* than those of the standard antibiotics, except for SAM 20 and CTX30. Similarly, they show weak effects against *Micrococcus luteus*. All the compounds have stronger antibacterial activity than those of the standard antibiotics P10, SAM20 and VA30 against *Pseudomonas aeruginosa*. *Proteus vulgaris* is the most sensitive bacterium towards the compounds, especially **4d**, having zone diameters of 15–21 mm. In general, all compounds show high anti-yeast activity against the yeast culture used in this study. While compound **4d** is the most effectual compound against the yeast cultures, *Kluyveromyces fragilis* is the most sensitive microorganism,

TABLE II. Antimicrobial activities of compounds (**4a–4d**) and some standard antibiotics and antifungal agents

Microorganisms	Inhibition zone/mm												
	Compounds				Antibiotics								
	<b>4a</b>	<b>4b</b>	<b>4c</b>	<b>4d</b>	P10	SAM20	CTX30	VA30	OFX5	TE30	NY100	KETO20	CLT10
<i>Escherichia coli</i>	10	12	12	14	18	12	10	22	30	28	–	–	–
<i>Staphylococcus aureus</i>	13	14	16	18	13	16	12	13	24	26	–	–	–
<i>Klebsiella pneumoniae</i>	13	14	15	17	18	14	13	22	28	30	–	–	–
<i>Pseudomonas aeruginosa</i>	12	11	14	16	8	10	54	10	44	34	–	–	–
<i>Proteus vulgaris</i>	15	19	18	21	10	16	18	20	28	26	–	–	–
<i>Bacillus cereus</i>	–	–	–	12	14	12	14	18	30	25	–	–	–
<i>Mycobacterium smegmatis</i>	–	–	–	–	15	21	11	20	32	24	–	–	–
<i>Listeria monocytogenes</i>	–	–	–	–	10	12	16	26	30	28	–	–	–
<i>Micrococcus luteus</i>	10	11	12	14	36	32	32	34	28	22	–	–	–
<i>Candida albicans</i>	13	14	17	19	–	–	–	–	–	–	20	21	15
<i>Kluyveromyces fragilis</i>	15	17	22	25	–	–	–	–	–	–	18	16	18
<i>Rhodotorula rubra</i>	14	16	15	23	–	–	–	–	–	–	18	22	16
<i>Hanseniaspora guilliermondii</i>	12	15	18	20	–	–	–	–	–	–	21	24	22
<i>Debaryomyces hansenii</i>	14	16	20	22	–	–	–	–	–	–	16	14	18

P10: Penicillin G (10 Units), SAM20: Ampicillin 10 µg, CTX30: Cefotaxime 30 µg, V30: Vancomycin 30 µg, OFX 5: Ofloxacin 5 µg, TE30: Tetracyclin 30 µg, N100: Nystatin 100 µg, KETO20: Ketoconazole 20 µg, CLT10: Clotrimazole 10 µg

having zone diameters of 15–25 mm. *Candida albicans* is more susceptible to compound **4d**, as compared to the standard antibiotics CLT10. Compound **4d** has a stronger anti-yeast activity against *Rhodotorula rubra* than all the tested standard antifungal agents. Notably, compounds **4c** and **4d** have higher anti-yeast activity against *Debaryomyces hansenii* than the standard antibiotics. Also *Hanseniaspora guilliermondii* is influenced at different levels.

The compounds differ significantly in their activity against the tested microorganisms. These differences may be attributed to fact that the cell wall in Gram-positive bacteria is single layered, whereas the Gram-negative cell wall is a multi-layered structure and the yeast cell wall is quite complex.<sup>34</sup>

#### EXPERIMENTAL

The <sup>1</sup>H- and <sup>13</sup>C-NMR spectra were recorded on a Bruker DPX FT-NMR spectrometer operating at 400 and 101.6 MHz, respectively. The <sup>1</sup>H and <sup>13</sup>C chemical shifts were measured using SiMe<sub>4</sub> as the internal standard. The infrared absorption spectra were recorded on a Perkin Elmer BX II spectrometer in KBr discs. The UV–Vis spectra were recorded on a Shimadzu 1201 series spectrometer. Electron impact ionization mass spectrometric (EI-MS) analyses were performed on a Thermo Finnigan-Trace DSQ spectrometer. Carbon, hydrogen and nitrogen analyses were performed on a Leco CHNS-932 C-, H-, N- analyzer. The melting points were measured on an Electro Thermal IA 9100 apparatus using a capillary tube. THF, EtOH, DMSO, DMF, CHCl<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub>, NaOH, K<sub>2</sub>CO<sub>3</sub>, benzene, formaldehyde, 4-nitrophenol, hydrazine hydrate, 2-hydroxybenzaldehyde, 3-hydroxybenzaldehyde, 4-hydroxybenzaldehyde and 2-hydroxy-1-naphthaldehyde and Pd–C (10 %) were purchased from Merck (Germany).

#### Synthesis of 2,2'-methylenebis[4-nitrophenol] (**1**)<sup>35,36</sup>

To formaldehyde (10 mL, 40 %) and H<sub>2</sub>O (6 mL) was added H<sub>2</sub>SO<sub>4</sub> (24 mL, 98 %). The mixture was stirred and heated at 80 °C. The hot mixture was added rapidly with stirring and heating to a solution of *p*-nitrophenol (38.0 g, 0.273 mol) in H<sub>2</sub>O (5 mL) at 75 °C. The mixture was heated under stirring at 130 °C for 1 h and then dissolved in NaOH (4 %). The solution was filtered and acidified with HCl, whereby the product separated. It was crystallized from acetic acid. The analytical and experimental data are summarized in Table III.

#### Synthesis of 2,11-dinitro-6,7-dihydro-13H-dibenzo[e,h][1,4]dioxonin (**2**)

To 2,2'-methylenebis [4-nitrophenol] (**1**) (3.718 g, 0.01113 mol) dissolved in DMF (150 mL, 99 %) was added 1,2-dibromoethane (2.081 g, 0.0113 mol). The mixture was stirred at reflux temperature for 24 h and then filtered. The solvent was removed under reduced pressure and the remaining yellow product was washed with water. The crude product was recrystallized from methanol. The analytical and experimental data are summarized in Table III.

#### Synthesis of 6,7-dihydro-13H-dibenzo[e,h][1,4]dioxonin-2,11 diamine (**3**)

To 2,11-dinitro-6,7-dihydro-13H-dibenzo[e,h][1,4]dioxonin (**2**) (0.5412 g, 0.00171 mol) and Pd/C (0.032 g, 10 %) dissolved in ethanol (150 mL, 99 %) was added dropwise hydrazine monohydrate (1.25 mL). The mixture was stirred at reflux temperature for 3 h and then filtered through a pad of celite to remove the catalyst. The solvent and excess hydrazine were removed *in vacuo* to give the crude product **3**, which was recrystallized from ethanol. The analytical and experimental data are summarized in Table III.

#### Synthesis of Schiff bases

7,13-Dihydro-6H-dibenzo[e,h][1,4]dioxonin-2,11-diamine (**3**) (0.0790 g, 0.0003 mol) was added to a dry THF (100 mL) solution of 2-hydroxybenzaldehyde (0.0763 g, 0.0006 mol). The



mixture was heated under stirring for 3 h. Compound 2,2'-(1*E*,1'*E*)-[(6,7-dihydro-13*H*-dibenzo[*e,h*][1,4]-dioxonin-2, 11-diyl)bis(nitrilomethylidyne)]diphenol (**4a**) was obtained by evaporation of the THF. It was crystallized from CHCl<sub>3</sub>:*n*-hexane (3:1).

The other Schiff bases 3,3'-(1*E*,1'*E*)-[(6,7-dihydro-13*H*-dibenzo[*e,h*][1,4]-dioxonin-2, 11-diyl)bis(nitrilomethylidyne)]diphenol (**4b**), 4,4'-(1*E*,1'*E*)-[(6,7-dihydro-13*H*-dibenzo[*e,h*][1,4]-dioxonin-2,11-diyl)bis(nitrilomethylidyne)]diphenol (**4c**) and 1,1'-(1*E*,1'*E*)-[(6,7-dihydro-13*H*-dibenzo[*e,h*][1,4]-dioxonin-2,11-diyl)bis(nitrilomethylidyne)]bis(2-naphthol) (**4d**) were obtained by the same method. The analytical and experimental details for all compounds are given in Table III.

TABLE III. Analytical and experimental data

Comp.	M.p. °C	Color	Yield %	C analysis/%		H analysis/%		N analysis/%	
				Calcd.	Exp.	Calcd.	Exp.	Calcd.	Exp.
<b>1</b>	272	pale-yellow	95	53.80	53.79	3.47	3.47	9.65	9.63
<b>2</b>	145	yellow	62	56.96	56.90	3.82	3.80	8.86	8.80
<b>3</b>	176	white-brown	91	70.29	70.31	6.29	6.25	10.93	10.93
<b>4a</b>	210	yellow	51	74.98	75.01	5.21	5.17	6.03	6.10
<b>4b</b>	190	black-brown	60	74.98	75.21	5.21	5.13	6.03	6.11
<b>4c</b>	238	white-yellow	86	74.98	75.08	5.21	5.13	6.03	6.01
<b>4d</b>	181	brown	75	78.71	78.70	5.00	5.03	4.96	4.98

#### Antimicrobial test

*Escherichia coli* ATCC 11230, *Staphylococcus aureus* ATCC 6538, *Klebsiella pneumoniae* UC57, *Micrococcus luteus* La 2971, *Proteus vulgaris* ATCC 8427, *Pseudomonas aeruginosa* ATCC 27853, *Mycobacterium smegmatis* CCM 2067, *Bacillus cereus* ATCC 7064, *Listeria monocytogenes* ATCC 15313, *Candida albicans* ATCC 10231, *Kluyveromyces fragilis* NRRL 2415, *Rhodotorula rubra* DSM 70403, *Debaryomyces hansenii* DSM 70238 and *Hanseniaspora guilliermondii* DSM 3432 were used as bacteria and yeast cultures. The compounds were dissolved in DMSO to a final concentration of 30 µg/mL. Empty sterilized antibiotic discs having a diameter of 6 mm (Schleicher & Schull No 2668, Germany) were each impregnated with 20 µL of solution. All the bacteria above-mentioned were incubated at 30±0.1 °C for 24 h by inoculation into Nutrient Broth (Difco), and the studied yeasts were incubated in Malt Extract Broth (Difco) for 48 h. An inoculum containing 10<sup>6</sup> bacterial cells or 10<sup>8</sup> yeast cells / mL was spread on Mueller–Hinton Agar (Oxoid) plates (1 mL inoculum / plate). The discs injected with solutions were placed on the inoculated agar by pressing slightly and incubated at 35 °C (24 h) for the bacteria, and at 25 °C (72 h) for the yeasts. On each plate, an appropriate reference antibiotic disc was applied depending on the test microorganisms.<sup>24,25</sup> The data reported in Table II are the average data of three experiments.

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## ИЗВОД

## СИНТЕЗА И АНТИМИКРОБНА АКТИВНОСТ НОВИХ КРУНА-ЕТАРА ТИПА ШИФОВЕ БАЗЕ

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Нови круна-етар лиганди типа Шифове базе (**4a–d**) синтетизовани су у реакцији 2-хидроксibenзалдехида, 3-хидроксibenзалдехида, 4-хидроксibenзалдехида и 2-хидрокси-1-нафталдехида са 6,7-дихидро-13H-добензо[e,h][1,4]диоксонин-2,11-диамином (**3**). Структура лиганда испитивана је елементалном анализом, као и UV-видљивом, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR и масеном спектрометријом. Антибактеријска активност и активност према гљивичним културама проверавана је према микроорганизмима: *Escherichia coli* ATCC 11230, *Staphylococcus aureus* ATCC 6538, *Klebsiella pneumoniae* UC57, *Micrococcus luteus* La 2971, *Proteus vulgaris* ATCC 8427, *Pseudomonas aeruginosa* ATCC 27853, *Mycobacterium smegmatis* CCM 2067, *Bacillus cereus* ATCC 7064 и *Listeria monocytogenes* ATCC 15313; *Candida albicans* ATCC 10231, *Kluyveromyces fragilis* NRRL 2415, *Rhodotorula rubra* DSM 70403, *Debaryomyces hansenii* DSM 70238 и *Hanseniaspora guilliermondii* DSM 3432.

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