

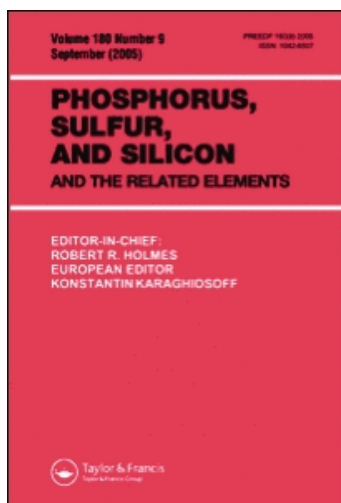
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Synthesis and Biological Evaluation of Some New Thioether-Ester Crown Ethers

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*New thioether-ester crown ethers have been synthesized starting from oxalyl chloride and different β,β' -dihydroxydithioethers. The synthesized compounds are screened for their antibacterial activity. Among the macrocyclic thioether-esters (5a–j), only 5,12-di[(allyloxy)methyl]-1,4-dioxo-7,10-dithiacyclododecane-2,3-dione (5e) and 5,12-di(isopropoxymethyl)-1,4-dioxo-7,10-dithiacyclododecane-2,3-dione (5f) were effective inhibitors against *Staphylococcus aureus* methicillin resistance and *Pseudomonas aeruginosa* with an MIC value of 525 and 265 μM . Structures of the synthesized compounds have been confirmed by ^1H NMR, ^{13}C NMR, and MS spectral studies.*

Keywords Dihydroxydithioethers; *Pseudomonas aeruginosa*; *Staphylococcus aureus*; thioether-ester crown ethers

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INTRODUCTION

β,β' -dihydroxydithioethers with two α,α' -substitutions have been recently synthesized.¹ The two secondary β,β' -dihydroxy groups make these compounds susceptible reagents to synthesize new thiocrown ethers possessing various sidearms.^{2,3} Biological activities of such sidearmed crownethers have been studied³ but no biological evaluations have been reported on β,β' -dihydroxydithioethers and their corresponding thiocrown ethers. In this article, we describe the synthesis of β,β' -dihydroxydithioether (**3a-j**) and their corresponding thioether-ester crown ethers (**5a-j**). The antibacterial activity of these compounds is also investigated.

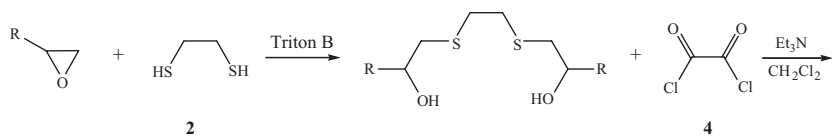
RESULTS

Synthesis

β,β' -dihydroxydithioether (**3a**) and the mixture of two diastereomers¹ of its derivatives (**3b-j**) were prepared by the action of two mole equivalents of oxiranes (**1a-j**) with dimercaptoehane (**2**) using benzyltrimethylammonium hydroxide (Triton B) as a catalyst¹ (Scheme 1). All dihydroxy compounds showed one spot on TLC except the (**3d**), which was a mixture and was purified by column chromatography (silica gel 60, 0.04–0.067 mm, hexane-ethylacetate 1:1). Treatment of dihydroxy compounds (**3a-i**) and (**3j**) with oxalyl chloride (**4**) under a basic condition of triethylamine in dried dichloromethane afforded 5,12-disubstituted 1,4-dioxo-7,10-dithiacyclododecane-2,3-diones (**5a-i**) and perhydrodibenzo[*e,k*][1,4,7,10]dioxadithiacyclododecane-6,7-dione (**5j**), respectively⁴ (Scheme 1).

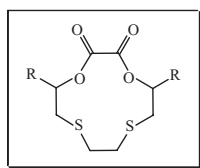
Biological Evaluations

Antibacterial activities of β,β' -dihydroxydithioethers (**3a-j**) and their corresponding thioether-ester crown ether (**5a-j**) were evaluated. MIC values, i.e., the lowest concentration of a drug that prevents growth of a particular pathogen,⁵ of (**3a-j**) and (**5a-j**) against two strains of bacteria *S. aureus* methicilin resistance and *P. aeruginosa* were measured. Ten isolated strains of *S. aureus* and *P. aeruginosa* from different organs of patients at the Microbiological Laboratory of Ghaem Hospital of Medical University of Mashhad–Iran were tested. Oxacillin (for *S. aureus*) and Gentamycin (for *P. aeruginosa*) were used as a positive control in all tests, and their MIC values were expressed in μM . Among the synthesized compounds (**3a-j**) and (**5a-j**), only (**5e**) and (**5f**) showed significant

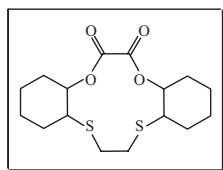
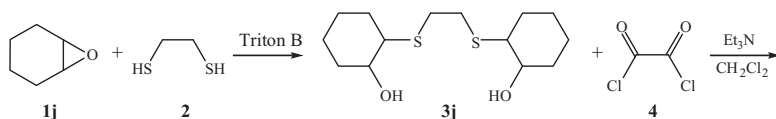


- 1a** R = H
1b R = CH₃
1c R = C₂H₅
1d R = Ph
1e R = CH₂OCH₂CHCH₂
1f R = CH₂OCH(CH₃)₂
1g R = CH₂O-*n*-C₄H₉
1h R = CH₂O-*tert*-C₄H₉
1i R = CH₂OPh

- 3a** R = H
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3i R = CH₂OPh



- 5a** R = H
5b R = CH₃
5c R = C₂H₅
5d R = Ph
5e R = CH₂OCH₂CHCH₂
5f R = CH₂OCH(CH₃)₂
5g R = CH₂O-*n*-C₄H₉
5h R = CH₂O-*tert*-C₄H₉
5i R = CH₂OPh



5j

SCHEME 1

activities against *S. aureus* and *P. aeruginosa* with MIC values of 525 and 265 μM (100 and 200 $\mu\text{g/mL}$). These results were compared with Gentamycin and Oxacillin activity with the standard MIC values of 16 and 32 $\mu\text{g/mL}$, respectively.

DISCUSSION

The ring opening of the starting oxiranes (**1b–i**) was region specific by a nucleophilic attack on the terminal carbon atoms affording secondary diols. This regioselectivity was not observed in the case of (**1d**), which gave a mixture of isomeric derivatives. Compounds (**3b–j**) were obtained as

a mixture of isomeric diastereomers. Their spectral data were perfectly consistent with the literature data.¹

Accordingly, compounds (**5b–j**) were obtained as a mixture of diastereomers, but the two stereogenic centers within the molecule were far from each other so they could not be discerned by the NMR technique. Their ¹H NMR spectrum showed a sharp singlet for the two methylene groups of the dimercaptoethane moiety. This is not the case for compound (**5j**) for which a multiplet was observed for these methylene groups. This may be explained if one assumes that the ring opening of cyclohexene oxide (**1j**) gave exclusively *trans*-diols, which were formed as an equimolar mixture of *meso*- and *threo*-.¹

The *S. aureus* methicillin resistance and *P. aeruginosa* have become a major nosocomial pathogen in communities, long-term-care facilities, and tertiary-care hospitals.^{6–9} Although (**5e**) and (**5f**) exhibited weak antibacterial activities against these pathogens in comparison with Gentamycin and Oxacillin, this study can be a beginning for the synthesis and evaluation of a new generation of antibacterial agents. Although both compounds of (**5e**) and (**5f**) are each a mixture of diastereomers,¹ if one can obtain a diastereomerically pure species of any of these compounds, the MIC value of pure diastereomer might be less or more than what we expected.

CONCLUSION

The aim of this study was to develop an efficient synthetic approach to construct various 5,12-disubstituted thioether-ester crown ethers and to screen for possible antibacterial activities. The efficient synthetic approach disclosed herein that led to quick output of a series of 1,4-dioxo-7,10-dithiacyclododecane-2,3-diones for the evaluation of antibacterial activities of these compounds indicated that only (**5e**) and (**5f**) can be considered the inhibitors for *S. aureus* methicillin resistance and *P. aeruginosa*.

EXPERIMENTAL

¹H NMR (500 MHz) and ¹³C NMR (125 MHz) were obtained by using a Bruker Avance DRX-500 fourier transformer spectrometer. Chemical shifts are reported in ppm (δ) downfield from tetramethylsilane (TMS). Electron impact mass spectra were recorded on a Varian Match 7A spectrometer. All chemicals were purchased from Merck and Fluka Co. and used without further purification.

General Procedure for the Synthesis of 1,4-dioxa-7,10-dithiacyclododecane-2,3-diones (5a–j)

A mixture of β,β' -dihydroxydithioether (3.0 mmoles) and triethylamine (0.65 g, 6.4 mmoles) in dried dichloromethane (10 mL) was cooled to 5–10°C. Oxalyl chloride (0.40 g, 3.1 mmoles) in dried dichloromethane (10 mL) was then added in one portion to the mixture while the mixture was allowed to warm to r. t. After 30 min, the mixture was poured into cold water (100 mL) and acidified with 5% HCl (20 mL). The aqueous solution was extracted with dichloromethane (2 \times 30 mL). The combined organic extracts were washed with 5% NaHCO₃ (2 \times 30 mL) and then brine (2 \times 30 mL), dried with Na₂SO₄, and concentrated under reduced pressure to provide the desired compounds. The purity of the compounds was checked on TLC (silica gel 60 F₂₅₄, dichloromethane-methanol 9:1).

General Procedure for Minimum Inhibitory Concentration

The Minimum Inhibitory Concentrations (MICs) of (3a–j) and (5a–j) were determined in the dilution tube-test method, which had been introduced by the National Committee for Clinical Laboratory Standards.¹⁰ For both dilution methods, decreasing concentrations of the antimicrobial agents to be tested, usually prepared in serial twofold dilution, were placed in tubes of a broth medium that supported the growth of the test microorganism. After sufficient incubation (usually overnight), the tubes were examined for turbidity, indicating growth of the microorganism. The organism grew in the tube that did not contain enough antimicrobial agent to inhibit growth. The lowest drug concentration of the agent that prevented growth of the test organism, as detected by lack of visual turbidity (matching the negative growth control), was designated the MIC. A serial dilution of the tested compounds (400 to 25 $\mu\text{g}/\text{mL}$) were added to the test bacteria in the Mueller–Hinton broth and were incubated at 37°C for 18–20 h. Growth was presented in the medium control and was absent from the inoculum control.¹¹

1,4-Dioxa-7,10-dithiacyclododecane-2,3-dione (5a)

White solid (54%), m.p.: 112°C; ¹H NMR: δ 2.84 (s, 4H, -SCH₂CH₂S-), 2.88 (t, J = 8 Hz, 4H, -SCH₂-), 4.45 (t, J = 8 Hz, 4H, -CH₂OCO); ¹³C NMR: δ 30.8 (-SCH₂CH₂S-), 32.6 (-SCH₂-), 68.3 (-CH₂OCO), 158.6 (C=O); MS m/z : 238 (M⁺), 148 (100%).

5,12-Dimethyl-1,4-dioxa-7,10-dithiacyclododecane-2,3-dione (5b)

White viscous liquid (65%); ¹H NMR: δ 1.45 (d, J = 8 Hz, 6H, -CH₃), 2.79–2.89 (m, 4H, -SCH₂-), 2.81 (s, 4H, -SCH₂CH₂S-), 5.13 (m, 2H,

CH-OCO); ^{13}C NMR: δ 21.9 (-CH₃), 32.3 (-SCH₂CH₂S-), 35.5 (-SCH₂-), 70.3 (CH-OCO), 157.7 (C=O); MS m/z : 264 (M⁺), 118 (100%).

5,12-Diethyl-1,4-dioxo-7,10-dithiacyclododecane-2,3-dione (5c)

White viscous liquid (69%); ^1H NMR: δ 1.00 (t, $J=8$ Hz, 6H, CH₃), 1.84 (m, 4H, -CH₂-), 2.78–2.87 (m, 4H, -SCH₂-), 2.82 (s, 4H, -SCH₂CH₂S-), 5.10 (m, 2H, CH-OCO); ^{13}C NMR: δ 9.8 (CH₃), 28.8 (-CH₂-), 32.3 (-SCH₂CH₂S-), 35.4 (-SCH₂-), 70.7 (CH-OCO), 157.5 (C=O); MS m/z : 292 (M⁺), 132 (100%).

5,12-Diphenyl-1,4-dioxo-7,10-dithiacyclododecane-2,3-dione (5d)

Yellow solid (70%), m.p.: 71–73°C; ^1H NMR: δ 2.84–2.93 (m, 4H, -SCH₂-), 2.85 (s, 4H, -SCH₂CH₂S-), 5.97 (m, 2H, CH-OCO), 7.14–7.34 (m, 10H, Ar-H); ^{13}C NMR: δ 32.7 (-SCH₂CH₂S-), 38.1 (-SCH₂-), 76.6 (CH-OCO), 127.5, 129.2, 130.2 and 137.7 (aromatic carbons), 157.7 (C=O); MS m/z : 388 (M⁺), 120 (100%).

5,12-Di(allyloxy)methyl-1,4-dioxo-7,10-dithiacyclododecane-2,3-dione (5e)

White viscous liquid (68%); ^1H NMR: δ 2.79–2.88 (m, 4H, -SCH₂-), 2.81 (s, 4H, -SCH₂CH₂S-), 3.72 (m, 4H, -OCH₂-), 4.06 (d, $J=6$ Hz, 4H, -CH₂O-), 5.07 (m, 2H, CH-OCO), 5.22 (dd, $J=10$ Hz, 1.2 Hz, 2H, *cis*), 5.30 (dd, $J=17$ Hz, 1.2 Hz, 2H, *trans*), 5.86–5.94 (m, 2H, -CH=); ^{13}C NMR: δ 33.1 (-SCH₂CH₂S-), 36.0 (-SCH₂-), 69.3 (-CH₂O-), 70.1 (-OCH₂), 72.9 (CH-OCO), 118.0 (=CH₂), 134.7 (-CH=), 158.3 (C=O); MS m/z : 376 (M⁺), 174 (100%).

5,12-Di(isopropoxymethyl)-1,4-dioxo-7,10-dithiacyclododecane-2,3-dione (5f)

White viscous liquid (70%); ^1H NMR: δ 1.21 (d, $J=6$ Hz, 6H, -CH₃), 2.80–2.89 (m, 4H, -SCH₂-), 2.84 (s, 4H, -SCH₂CH₂S-), 3.63 (m, 2H, -O-CH), 3.71 (m, 4H, -CH₂O-), 5.20 (m, 2H, CH-OCO); ^{13}C NMR: δ 22.4 (-CH₃), 33.1 (-SCH₂CH₂S-), 36.1 (-SCH₂-), 70.1 (-O-CH), 71.0 (-CH₂O-), 72.7 (CH-OCO), 158.2 (C=O); MS m/z : 388 (M⁺), 120 (100%).

5,12-Di(butoxymethyl)-1,4-dioxo-7,10-dithiacyclododecane-2,3-dione (5g)

White viscous liquid (51%); ^1H NMR: δ 0.89 (t, $J=8$ Hz, 6H, -CH₃), 1.18–1.69 (m, 8H, -CH₂CH₂-), 2.75–2.91 (m, 4H, -SCH₂-), 2.81 (s, 4H, -SCH₂CH₂S-), 3.47 (t, $J=8$ Hz, 4H, -OCH₂-), 3.70 (m, 4H, -CH₂O-), 5.15 (m, 2H, CH-OCO); ^{13}C NMR: δ 14.4 (-CH₃), 19.3 (-CH₂-), 31.2 (-CH₂-),

33.1 (-SCH₂CH₂S-), 36.0 (-SCH₂-), 70.3 (-OCH₂-), 71.1 (-CH₂O-), 72.6 (CH-OCO), 158.1 (C=O); MS *m/z*: 408 (M⁺), 190 (100%).

5,12-Di(tert-butoxymethyl)-1,4-dioxa-7,10-dithiacyclododecane-2,3-dione (5h)

White viscous liquid (53%); ¹H NMR: δ 1.17 (s, 18H, -CH₃), 2.80–2.90 (m, 4H, -SCH₂-), 2.81 (s, 4H, -SCH₂CH₂S-), 3.67 (m, 4H, -CH₂O-), 5.12 (m, 2H, CH-OCO); ¹³C NMR δ 27.4 (-CH₃), 33.2 (-SCH₂CH₂S-), 36.0 (-SCH₂-), 70.4 (-O-C), 71.3 (-CH₂O-), 72.8 (CH-OCO), 158.2 (C=O); MS *m/z*: 408 (M⁺), 190 (100%).

5,12-Di(phenoxyethyl)-1,4-dioxa-7,10-dithiacyclododecane-2,3-dione (5i)

White solid (63%), m.p.: 155–157°C; ¹H NMR: δ 2.78–2.91 (m, 4H, -SCH₂-), 2.81 (s, 4H, -SCH₂CH₂S-), 4.25 (m, 4H, -CH₂O-), 5.35 (m, 2H, CH-OCO), 6.77–7.30 (m, 10H, Ar-H); ¹³C NMR: δ 33.1 (-SCH₂CH₂S-), 36.3 (-SCH₂-), 71.9 (-CH₂O-), 73.5 (CH-OCO), 158.5 (C=O); MS *m/z*: 448 (M⁺), 210 (100%).

Perhydrodibenzo[e,k][1,4,7,10]dioxadithiacyclododecane-6,7-dione (5j)

White solid (64%), m.p.: 82–84°C; ¹H NMR: δ 1.29–1.62 (m, 8H, -CH₂CH₂-), 1.76 (m, 4H, -CH₂-), 2.14 (m, 4H, -CH₂-), 2.79–2.94 (m, 6H, -SCH- and -SCH₂CH₂S-), 4.88 (m, 2H, CH-OCO), ¹³C NMR: δ 24.8 (-CH₂-), 26.4 (-CH₂-), 30.7 and 31.9 (-CH₂-), 32.5 and 33.7 (-CH₂-), 33.4 and 34.5 (-SCH₂-CH₂S-), 47.4 and 48.0 (-SCH-), 79.4 and 80.0 (CH-OCO), 157.3 and 157.5 (C=O); MS *m/z*: 344 (M⁺), 158 (100%).

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