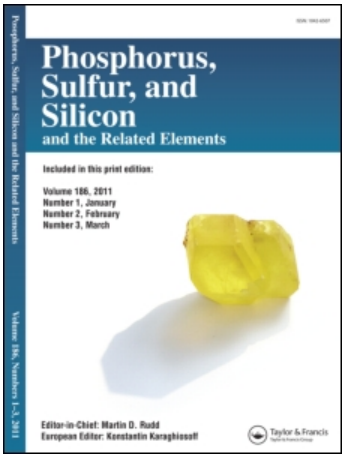

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Synthesis and Biological Evaluation of Some New Thioether-Ester Crown Ethers

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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-dioxa-7,10-dithiacyclododecane-2,3-dione (**5e**) and 5,12-di(isopropoxymethyl)-1,4-dioxa-7,10-dithiacyclododecane-2,3-dione (**5f**) were effective inhibitors against* Staphilococcus aureus *methicillin resistance and* Pseudomanas aeruginosa *with an MIC value of 525 and 265 μM. Structures of the synthesized compounds have been confirmed by ^{1}H NMR, ^{13}C NMR, and MS spectral studies.*

Keywords Dihydroxydithioethers; *Pseudomanas aeruginosa; Staphilococcus aureus*; thioether-ester crown ethers

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INTRODUCTION

β,β'-dihydroxydithioethers with two α,α'-substations 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 studied[3] 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.

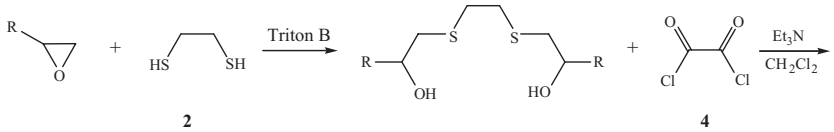
RESULTS

Synthesis

β,β'-dihydroxydithioether (**3a**) and the mixture of two diastreomrers[1] 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 catalyst[1] (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 triehtylamine in dried dichloromethane afforded 5,12-disubstituted 1,4-dioxa-7,10-dithiacyclododecane-2,3-diones (**5a–i**) and perhydrodibenzo[*e*,*k*][1,4,7,10]dioxadithiacyclododecine-6,7-dione (**5j**), respectively[4] (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



2 **4**

1a R = H
1b R = CH_3
1c R = C_2H_5
1d R = Ph
1e R = $CH_2OCH_2CHCH_2$
1f R = $CH_2OCH(CH_3)_2$
1g R = CH_2O-*n*-C_4H_9
1h R = CH_2O-*tert*-C_4H_9
1i R = CH_2OPh

3a R = H
3b R = CH_3
3c R = C_2H_5
3d R = Ph
3e R = $CH_2OCH_2CHCH_2$
3f R = $CH_2OCH(CH_3)_2$
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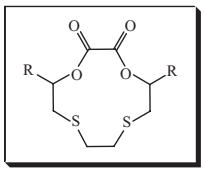

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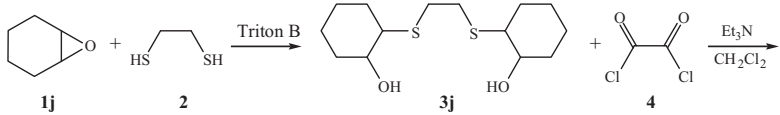
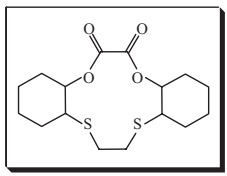


1j **2** **3j** **4**



5j

SCHEME 1

activities against *S. aureus* and *P. aeruginosa* with MIC values of 525 and 265 μM (100 and 200 μg/mL). These results were compared with Gentamycin and Oxacillin activity with the standard MIC values of 16 and 32 μg/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 regiospecifity 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 ^{1}H 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 diastreomers,[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-dioxa-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

^{1}H NMR (500 MHz) and ^{13}C 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 (2×30 mL). The combined organic extracts were washed with 5% $NaHCO_3$ (2×30 mL) and then brine (2×30 mL), dried with Na_2SO_4, and concentrated under reduced pressure to provide the desired compounds. The purity of the compounds was checked on TLC (silica gel 60 F_{254}, 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 μg/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; ^{1}H NMR: δ 2.84 (s, 4H, -SCH_2CH_2S-), 2.88 (t, $J = 8$ Hz, 4H, -SCH_2-), 4.45 (t, $J = 8$ Hz, 4H, -CH_2OCO); ^{13}C NMR: δ 30.8 (-SCH_2CH_2S-), 32.6 (-SCH_2-), 68.3 (-CH_2OCO), 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%); ^{1}H NMR: δ 1.45 (d, J = 8 Hz, 6H, -CH_3), 2.79–2.89 (m, 4H, -SCH_2-), 2.81 (s, 4H, -SCH_2CH_2S-), 5.13 (m, 2H,

CH-OCO); ^{13}C NMR: δ 21.9 (-CH_3), 32.3 (-SCH_2CH_2S-), 35.5 (-SCH_2-), 70.3 (CH-OCO), 157.7 (C=O); MS m/z: 264 (M+), 118 (100%).

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

White viscous liquid (69%); ^{1}H NMR: δ 1.00 (t, J = 8 Hz, 6H, CH_3), 1.84 (m, 4H, -CH_2-), 2.78–2.87 (m, 4H, -SCH_2-), 2.82 (s, 4H, -SCH_2CH_2S-), 5.10 (m, 2H, CH—OCO); ^{13}CNMR: δ 9.8 (CH_3), 28.8 (-CH_2-) 32.3 (-SCH_2CH_2S-), 35.4 (-SCH_2-), 70.7 (CH-OCO), 157.5 (C=O); MS *m/z*: 292 (M+), 132 (100%).

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

Yellow solid (70%), m.p.: 71–73°C; ^{1}H NMR: δ 2.84–2.93 (m, 4H, -SCH_2-), 2.85 (s, 4H, -SCH_2CH_2S-), 5.97 (m, 2H, CH—OCO), 7.14–7.34 (m, 10H, Ar-H); ^{13}CNMR: δ 32.7 (-SCH_2CH_2S-), 38.1 (-SCH_2-), 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-dioxa-7,10-dithiacyclododecane-2,3-dione (5e)

White viscous liquid (68%); ^{1}H NMR: δ 2.79–2.88 (m, 4H, -SCH_2-), 2.81 (s, 4H, -SCH_2CH_2S-), 3.72 (m, 4H, -OCH_2-), 4.06 (d, J = 6 Hz, 4H, -CH_2O-), 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 (-SCH_2CH_2S-), 36.0 (-SCH_2-), 69.3 (-CH_2O-), 70.1 (-OCH_2), 72.9 (CH—OCO), 118.0 (=CH_2), 134.7 (-CH=), 158.3 (C=O); MS *m/z*: 376 (M+), 174 (100%).

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

White viscous liquid (70%); ^{1}H NMR: δ 1.21 (d, J = 6 Hz, 6H, -CH_3), 2.80–2.89 (m, 4H, -SCH_2-), 2.84 (s, 4H, -SCH_2CH_2S-), 3.63, (m, 2H, -O—CH), 3.71 (m, 4H, -CH_2O-), 5.20 (m, 2H, CH—OCO); ^{13}CNMR: δ 22.4 (-CH_3), 33.1 (-SCH_2CH_2S-), 36.1 (-SCH_2-), 70.1 (-O-CH), 71.0 (-CH_2O-), 72.7 (CH-OCO), 158.2 (C=O); MS *m/z*: 388 (M+), 120 (100%).

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

White viscous liquid (51%); ^{1}H NMR: δ = 0.89 (t, J = 8 Hz, 6H, -CH_3), 1.18–1.69 (m, 8H, -CH_2CH_2-), 2.75–2.91 (m, 4H, -SCH_2-), 2.81 (s, 4H, -SCH_2CH_2S-), 3.47, (t, J = 8 Hz, 4H, -OCH_2-), 3.70 (m, 4H, -CH_2O-), 5.15 (m, 2H, CH—OCO); ^{13}CNMR: δ 14.4 (-CH_3), 19.3 (-CH_2-), 31.2 (-CH_2-),

33.1 (-SCH_2CH_2S-), 36.0 (-SCH_2-), 70.3 (-OCH_2-), 71.1 (-CH_2O-), 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%); ^{1}H NMR: δ 1.17 (s, 18H, -CH_3), 2.80–2.90 (m, 4H, -SCH_2-), 2.81 (s, 4H, -SCH_2CH_2S-), 3.67 (m, 4H, -CH_2O-), 5.12 (m, 2H, CH-OCO); ^{13}CNMR δ 27.4 (-CH_3), 33.2 (-SCH_2CH_2S-), 36.0 (-SCH_2-), 70.4 (—O—C), 71.3 (-CH_2O-), 72.8 (CH—OCO), 158.2 (C=O); MS *m/z*: 408 (M+), 190 (100%).

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

White solid (63%), m.p.: 155–157°C; ^{1}H NMR: δ 2.78–2.91 (m, 4H, -SCH_2-), 2.81 (s, 4H, -SCH_2CH_2S-), 4.25 (m, 4H, -CH_2O-), 5.35 (m, 2H, CH-OCO), 6.77–7.30 (m, 10H, Ar-H); ^{13}CNMR: δ 33.1 (-SCH_2CH_2S-), 36.3 (-SCH_2-), 71.9 (-CH_2O-), 73.5 (CH-OCO), 158.5 (C=O); MS *m/z*: 448 (M+), 210 (100%).

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

White solid (64%), m.p.: 82–84°C; ^{1}H NMR: δ 1.29–1.62 (m, 8H, -CH_2CH_2-), 1.76 (m, 4H, -CH_2-), 2.14 (m, 4H, -CH_2-), 2.79–2.94 (m, 6H, -SCH- and -SCH_2CH_2S-), 4.88 (m, 2H, CH—OCO), ^{13}CNMR: δ 24.8 (-CH_2-), 26.4 (-CH_2-), 30.7 and 31.9 (-CH_2-), 32.5 and 33.7 (-CH_2-), 33.4 and 34.5 (-SCH_2-CH_2S-), 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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