Hindawi
Journal of Chemistry
Volume 2018, Article ID 3589342, 14 pages
https://doi.org/10.1155/2018/3589342

Research Article

Synthesis and Antifungal Activity of β-Hydroxysulfides of 1,3-Dioxepane Series

Roman S. Pavelyev,[1] **Rusalia M. Vafina**,[1] **Konstantin V. Balakin**,[1,2] **Oleg I. Gnezdilov**,[3] **Aleksey B. Dobrynin**,[4] **Olga A. Lodochnikova**,[4] **Rashid Z. Musin**,[4] **Galina A. Chmutova**,[1] **Svetlana A. Lisovskaya**,[5] **and Liliya E. Nikitina**[6]

[1]*Kazan (Volga Region) Federal University, Kremlyovskaya 18, Kazan 420008, Russia*
[2]*I.M. Sechenov First Moscow State Medical University, Trubetskaya 8, Bldg 2, Moscow 119991, Russia*
[3]*Kazan E. K. Zavoisky Physical-Technical Institute of the Russian Academy of Sciences, Sibirsky Tract, 10/7, Kazan 420029, Russia*
[4]*A.E. Arbuzov Institute of Organic and Physical Chemistry; KazSC, Russian Academy of Sciences, Arbuzova 8, Kazan 420088, Russia*
[5]*Kazan Scientific and Research Institute of Epidemiology and Microbiology, Bolshaya Krasnaya 67, Kazan 420015, Russia*
[6]*Kazan State Medical University, Butlerova 49, Kazan 420012, Russia*

Correspondence should be addressed to Roman S. Pavelyev; rpavelyev@gmail.com

Received 6 March 2018; Revised 11 July 2018; Accepted 25 July 2018; Published 10 October 2018

Academic Editor: Maria F. Carvalho

Synthesis of β-hydroxysulfides of 1,3-dioxepane series and their further functionalization were performed. Chiral β-hydroxysulfides were separated into enantiomers using enzymatic acylation by lipase PS. Study of antifungal activity of the obtained compounds showed that some enantiomerically pure 6-arylthio-1,3-dioxepan-5-ols represent promising antifungal drug candidates.

1. Introduction

β-Hydroxysulfides are attractive tools in organic synthesis, which are actively used in the synthesis of allylic alcohols, cyclic sulfides, thioketones, and physiologically active compounds [1–5]. Products of their oxidation, β-hydroxysulfones, are useful reagents for preparation of lactones [6], 2,5-disubstituted tetrahydrofuranes [7], and vinyl sulfones [8]. Compounds containing phenylsulfonyl fragment are also widely used in organic synthesis [9].

Various 5- and 6-substituted 1,3-dioxepanes are relatively scarce chemotype in medicinal chemistry due to synthetic difficulties and stability issues under physiological conditions. Nevertheless, in several reports, they were described as promising physiologically active compounds. Thus, a series of 5-hydroxy-6-sulfonamido-1,3-dioxepanes were reported as hypoglycemic agents which were active in mice with diabetes [10]. The same group of researchers reported several *N*-sulfonyl-tetrahydro[1, 3]dioxepino[5, 6] azirines which also possessed hypoglycemic activity [11]. Optically active derivatives of 1,3-dioxepan-5-ol were described as flexible analogs of a known HIV-1 protease inhibitor (PI) darunavir [12]. They demonstrated excellent potency against a variety of multi-PI-resistant clinical strains, and the structure-activity studies indicated that the ring size, stereochemistry, and position of oxygens were important for the observed activity.

In attempt to combine the β-hydroxysulfide and 1,3-dioxepane structural motifs, we previously synthesized a series of 2-phenyl-6-arylthio-1,3-dioxepan-5-ols, which possessed a moderate antifungal activity [13]. In order to optimize structure-activity parameters of this interesting structural chemotype, in this work we have prepared a series of novel chiral β-hydroxysulfides of 1,3-dioxepane series and

studied their antifungal activity against a panel of pathogenic microscopic fungi. It should be noted that microscopic fungi (micromycetes), causing mycoses, are significantly different from other infectious agents. Fungi are eukaryotic and are characterized by the presence of a rigid outer wall. Micromycetes are classified according to morphological characteristics, the degree of pathogenicity, and the ability to cause diseases of various organs and systems. In this work, we used four aggressive clinical isolates of *Candida albicans*, *Aspergillus fumigatus*, *Epidermophyton floccosum*, and *Mucor pusillus* species. Among mycelial pathogens of invasive mycoses, *Aspergillus* spp. are the most widespread. Dermatomycetes (*Epidermophyton* spp.) are one of the most common causative agents of superficial mycoses of skin, hair, and nails. Zygomycetes (*Mucor* spp.) cause extremely severe invasive mycoses with a very high mortality rate. And, finally, the vast majority of cases of fungal lesions of mucous membranes can be attributed to infections caused by yeast fungi of *Candida* species.

2. Materials and Methods

2.1. General Information. Chromatographic purification of compounds was carried out using column chromatography on Acros silica gel (60–200 mesh). Reaction progress and purity of compounds were monitored by TLC on Sorbfil PTLC-AF-A-UF plates.

Melting points of the products were determined using a Stanford Research Systems M.P.A-100 OptiMelt apparatus.

^{1}H and ^{13}C NMR spectra were recorded on a "Bruker AVANCE 400" at operating frequency 400 and 100 MHz, respectively, using TMS as an internal standard.

Gas chromatography/mass spectrometry experiments were performed using DFS "Thermo Electron Corporation" apparatus. The following experimental conditions for mass spectrometry measurements were used: method of ionization: electron ionization; electron energy: 70 eV; and ion source temperature: 280°C. For gas chromatography analysis, a capillary column DB-5MS (30 × 0.25) was used with helium as the gas carrier. The following experimental conditions were applied: gas-carrier rate 1 ml/min; injector temperature 250°C; temperature gradient: 50°C (1 min)-6 grad/min-120°C-20 grad/min-280°C (15 min); and sample volume 0.3 μl.

HPLC experiment was performed using the Chiralpak AGP column (15.0 × 0.4 sm, 5 μm). A solution of methanol and 0.01 M ammonium acetate buffer (1 : 99 v/v) was used as the eluent. The elution rate was 0.9 ml/min, and the product was detected spectrophotometrically at 250 nm.

MALDI-TOF experiments were performed using an ULTRAFLEX III TOF/TOF mass spectrometer (Bruker Daltonik GmbH, Germany). The spectra of positive ions were recorded in linear mode with ion acceleration up to 20 keV. The energy of the laser beam was attenuated down to 70% of the full laser power. Analyte and *p*-nitroaniline matrix compounds were dissolved in acetone (1% in case of matrix and 0.1% in case of analyte) using glassware. The samples were prepared by a "dried-droplet" method: 0.3 μl droplets of the solutions were deposited on the marked spots on the standard target plate "AnchorChip" (Bruker Daltonik GmbH, Germany) and left to dry.

For analyzing optically active substances, "ADP 440" (B + S) polarimeter was used.

Quantum-chemical calculations were performed by DFT method B3LYP/6-31G(d,p) using Gaussian-98 [14] program with full geometry optimization without restrictions on symmetry, and a matrix of second derivatives was calculated for all stationary points. All discussed structures have only positive frequencies. Scaling factors [15] were not introduced.

Compounds **2** [16], **11** [17], **12** [18], **13** [19], **14** [20], and **19** [28] were prepared according to previously described methods with insignificant modifications.

2.2. Experimental Details

*2.2.1. 3,5,8-Trioxabicyclo[5.1.0]octane (**2**).* Oxone (169 mmol) was slowly added by portions to a stirred solution of 1,3-dioxacyclohept-5-en **1** (130.2 mmol) and $NaHCO_3$ (619 mmol) in 100 ml of acetone-water mixture (1 : 1 v/v) for 3 hours at 20°C. Then, the reaction mixture was additionally stirred for 1 hour. The product was extracted with CH_2Cl_2 (2 × 50 ml). Organic layers were combined and dried over $MgSO_4$. The solvent was evaporated under reduced pressure, and the product was purified by column chromatography on silica gel (eluent petroleum ether-ethyl acetate, 7 : 1). Yield 75%, colorless crystals, m.p. 56°C–57°C.

*2.2.2. 6-(Phenylthio)-1,3-dioxepan-5-ol (**3**).* (1) General Procedure for Preparation of β-Hydroxysulfides 3, **21**–**23**

A mixture of thiophenol (2.7 mmol), K_2CO_3 (0.15 mmol), and epoxide (2.6 mmol) was heated until the appearance of the first bubbles. The heating source was removed, and a short-time (<1 minute) spontaneous boiling-up with a sharp increase of the temperature was observed. The reaction mixture was cooled, and the product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 4 : 1).

Yield 93%, colorless oil. ^{1}H NMR ($CDCl_3$), δ: 3.13 br. s (1H, OH), 3.23–3.27 m (1H, H^6, $^3J(H^6\ H^5) = 5.5$ Hz, $^3J(H^6\ H^7{}_A) = 6.5$ Hz, $^3J(H^6\ H^7{}_B) = 2.7$ Hz), 3.69–3.75 m (1H, H^5, $^3J(H^5\ H^4{}_A) = 6.0$ Hz, $^3J(H^5\ H^4{}_B) = 1.7$ Hz), 3.75–3.79 m (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.0$ Hz), 3.81–3.88 m (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.5$ Hz), 4.04–4.12 m (2H, $H^7{}_B$, $H^4{}_B$), 4.74 and 4.77 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.5$ Hz), 7.24–7.48 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 54.63 (C^6), 65.32 (C^7), 66.39 (C^4), 71.34 (C^5), 94.07 (C^2), 127.32 (C_{Ar}), 129.05 (C_{Ar}), 131.73 (C_{Ar}), 133.22 (C_{Ar}). MS (EI): m/z (%) = 226 (M^+, 56).

*2.2.3. 6-(Phenylsulfonyl)-1,3-dioxepan-5-ol (**4**).* Oxone (2.0 mmol) was added by portions for 1.5 hour to a stirred solution of sulfides (1.5 mmol) and $NaHCO_3$ (7.3 mmol) in 20 ml of acetone-water mixture (1 : 1, v/v). The reaction mixture was stirred for 1 hour, then $CHCl_3$ (100 ml) was added. The aqueous layer was separated, saturated with

NaCl, and extracted with $CHCl_3$. Organic phases were combined and dried over $MgSO_4$. The product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 2 : 1).

Yield 85%, colorless oil. ^{1}H NMR ($CDCl_3$), δ: 3.24 br. s (1H, OH), 3.30–3.36 m (1H, H^6, $^3J(H^6\ H^5) = 6.75$ Hz, $^3J(H^6\ H^7{}_B) = 3.65$ Hz, $^3J(H^6\ H^7{}_A) = 8.14$ Hz), 3.73–3.80 m (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.23$ Hz, $^3J(H^4{}_A\ H^5) = 7.1$ Hz), 3.81–3.88 m (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.8$ Hz), 3.96–4.04 m (2H, $H^7{}_B$, $H^4{}_A$, $^3J(H^4{}_B\ H^5) = 3.3$ Hz), 4.26 dt (1H, H^5, $^3J(H^5\ OH) = 3.0$ Hz), 4.60 and 4.71 (AB, 2H, $2H^2$, $^2J(H^2{}_B\ H^2{}_A) = -4.82$ Hz), 7.57–7.94 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 61.57 (C^7), 67.91 (C^5), 68.59 (C^4), 69.96 (C^6), 95.07 (C^2), 128.72 (C_{Ar}), 129.57 (C_{Ar}), 134.51 (C_{Ar}), 137.41 (C_{Ar}). MALDI-MS: 259 $[M + H]^+$, 281 $[M + Na]^+$, 297 $[M + K]^+$.

*2.2.4. 6-(Phenylthio)-1,3-dioxepan-5-yl Acetate (**5**).* Ac_2O (7.5 mmol), Et_3N (7.5 mmol), and DMAP (0.05 mmol) were successively added to a stirred solution of hydroxyl sulfide (5 mmol) in 20 ml of CH_2Cl_2, and the reaction mixture was stirred for 1 hour. Then, the solvent was evaporated under reduced pressure, and the product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 7 : 1).

Yield 96%, colorless oil. ^{1}H NMR ($CDCl_3$), δ: 2.02 s (3H, CH_3), 3.33 dt (1H, H^6, $^3J(H^6\ H^5) = 5.7$ Hz, $^3J(H^6\ H^7{}_A) = 6.35$ Hz, $^3J(H^6\ H^7{}_B) = 2.5$ Hz), 3.78 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.3$ Hz), 3.82 dd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.6$ Hz, $^3J(H^4{}_A\ H^5) = 5.5$ Hz), 3.99 dd (1H, $H^4{}_B$, $^3J(H^4{}_B\ H^5) = 2.4$ Hz), 4.09 dd (1H, $H^7{}_B$), 4.63 and 4.75 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.5$ Hz), 4.91 m (1H, H^5), 7.18–7.47 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 20.53 (CH_3), 51.59 (C^6), 64.94 ($C^{7(4)}$), 65.01 ($C^{4(7)}$), 73.30 (C^5), 93.91 (C^2), 127.01 (C_{Ar}), 128.69 (C_{Ar}), 131.46 (C_{Ar}), 133.07 (C_{Ar}), 169.42 (CO). MS (EI): m/z (%) = 268 (M^+, 5).

*2.2.5. 6-(Phenylsulfonyl)-1,3-dioxepan-5-yl Acetate (**6**).* Oxone (2.0 mmol) was added by portions for 1.5 hour to a stirred solution of sulfides (1.5 mmol) and $NaHCO_3$ (7.3 mmol) in 20 ml of acetone-water mixture (1 : 1, v/v). The reaction mixture was stirred for 1 hour, and then $CHCl_3$ (20 ml) was added. The aqueous layer was separated, saturated with NaCl, and extracted with $CHCl_3$. Organic layers were combined and dried over $MgSO_4$. The product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 7 : 1).

Yield 80%, colorless crystals, m.p. 88°C–89°C. ^{1}H NMR ($CDCl_3$), δ: 1.84 s (3H, CH_3), 3.48–3.53 m (1H, H^6, $^3J(H^6\ H^5) = 5.6$ Hz, $^3J(H^6\ H^7{}_A) = 6.88$ Hz, $^3J(H^6\ H^7{}_B) = 3.03$ Hz), 3.87–3.97 m (2H, $H^4{}_A$, $H^4{}_B$, $^2J(H^4{}_A\ H^4{}_B) = -13.06$ Hz, $^3J(H^4{}_A\ H^5) = 4.9$ Hz, $^3J(H^4{}_B\ H^5) = 2.75$ Hz), 4.13 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.96$ Hz), 4.36 dd (1H, $H^7{}_B$), 4.63 and 4.81 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -5.16$ Hz), 5.34 m (1H, H^5), 7.56–7.95 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 20.62 (CH_3), 61.83 (C^7), 67.83 (C^6), 67.94 (C^4), 69.58 (C^5), 95.90 (C^2), 128.84 (C_{Ar}), 129.33 (C_{Ar}), 134.18 (C_{Ar}), 138.19 (C_{Ar}), 169.42 (CO). MALDI-MS: 301 $[M + H]^+$, 323 $[M + Na]^+$, 339 $[M + K]^+$.

*2.2.6. 5-(Phenylsulfonyl)-4,7-dihydro-1,3-dioxepine (**7**).* K_2CO_3 (9 mmol) was added to a solution of acetate **5** (3 mmol) in 20 ml of methanol. The mixture was stirred for 1 hour, K_2CO_3 was filtered off, and then the solvent was removed. The product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 1 : 1).

Yield 95%, colorless crystals, m.p. 86°C–87°C. ^{1}H NMR ($CDCl_3$), δ: 4.41–4.45 br. m (2H, H^4), 4.45–4.48 br. m (2H, H^7), 4.82 s (2H, H^2), 7.02 t (1H, H^6, $^3J(H^6\ H^7) = 3.3$ Hz), 7.51–7.88 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 63.80 (C^7), 65.95 (C^4), 96.58 (C^2), 128.01 (C_{Ar}), 129.54 (C_{Ar}), 133.81 (C_{Ar}), 139.20 (C_{Ar}), 141.35 (C^6), 143.52 (C^5). MALDI-MS: 241 $[M + H]^+$.

*2.2.7. cis-2,3-Epoxybutane-1,4-diol (**11**).* Compound **11** was obtained from compound **10** (1.76 g, 20 mmol) using a procedure similar to that used for the synthesis of epoxide **2**. Yield 85% (1.77 g), colorless crystals, m.p. 50–51°C.

*2.2.8. 3-(Phenylthio)butane-1,2,4-triol (**12**).* A mixture of epoxide **11** (1.77 g, 17 mmol), thiophenol (1.91 ml, 18.7 mmol), and DABCO (0.019 g, 0.17 mmol) in 50 ml of water was heated on an oil bath (90°C) under stirring. The reaction was monitored by TLC. The reaction mixture was extracted with CH_2Cl_2 (3×15 ml), and the organic layers were combined and dried over $MgSO_4$. The product was purified by column chromatography (eluent acetone). Yield 82%, colorless crystals, m.p. 91–92°C.

*2.2.9. (Z)-4-Hydroxybut-2-en-1-yl Acetate (**13**).* A solution of Ac_2O (5.1 g, 50 mmol) in 40 ml of CH_2Cl_2 was slowly added to a stirred solution of diol **10** (5.35 g, 60.72 mmol) and Et_3N (5.06 g, 50.1 mmol) in 120 ml of CH_2Cl_2, and the reaction mixture was stirred for an additional 1 hour. Then, the reaction mixture was washed with saturated aqueous solutions of $NaHCO_3$ (50 ml) and NaCl (2×50 ml), and the organic layer was dried over $MgSO_4$. The product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 4 : 1). Yield 58%. The spectral data for the obtained compound completely correspond to those reported in literature [19].

*2.2.10. (3-(Hydroxymethyl)oxirane-2-yl)methyl Acetate (**14**).* Compound **14** was obtained from compound **13** (1.41 g, 10.6 mmol) using a procedure similar to that used for the synthesis of epoxide **2**. Yield 70% (1.1 g), colorless oil. The spectral data for the obtained compound completely correspond to those reported in literature [20].

*2.2.11. 3,4-Dihydroxy-2-(phenylthio)butyl Acetate (**16**) and 2,4-Dihydroxy-3-(phenylthio)butyl Acetate (**15**).* Compounds **15** and **16** were obtained from epoxide **14** (0.57 g, 3.85 mmol) using a procedure similar to that used for the synthesis of dioxepane **3**. An inseparable mixture of isomers **15** and **16** in 1 : 1 ratio was obtained as clear oil. Yield 63% (0.63 g). Mass spectrum (EI) m/z (%): 256 (M^+, 83).

*2.2.12. (5-(Phenylthio)-1,3-dioxan-4-yl)methanol (**9**).* A mixture of acetates **15** and **16** (3.0 g, 11.72 mmol), paraformaldehyde (1.0 g), and calcined copper sulfate (1.0 g) in CH_2Cl_2 in the presence of catalytic amounts of *p*-toluenesulfonic acid was stirred at 20°C for 48 hours. Copper sulfate was removed by filtration, and the solvent was removed under vacuum. The product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 5 : 1).

Yield 24%, colorless crystals, m.p. 85°C–86°C. ^{1}H NMR ($CDCl_3$), δ: 2.2 br. s (1H, OH), 3.06–3.09 m (1H, H^5, $^3J(H^5\ H^4) = 2.3$ Hz, $^3J(H^5\ H^6{}_A) = 2.0$ Hz, $^3J(H^5\ H^6{}_B) = 1.8$ Hz), 3.59 dd (1H, $CH_A\ H_BOH$, $^2J(CH_AH_BOH\ CH_AH_BOH) = -11.7$ Hz, $^3J(CH_AH_BOH\ H^4) = 4.7$ Hz), 3.80–3.87 m (2H, $H^6{}_A$, CH_AH_BOH, $^2J(H^6{}_A\ H^6{}_B) = -11.8$ Hz, $^4J(H^6{}_A\ H^2{}_B) = -1.0$ Hz, $^3J(CH_AH_BOH\ H^4) = 7.7$ Hz), 3.93–3.97 m (1H, H^4), 3.99–4.04 m (1H, $H^6{}_B$), 4.64 and 5.03 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -6.3$ Hz), 7.07–7.35 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 47.27 (C^5), 63.80 (CH_2OH), 70.86 (C^6), 79.48 (C^4), 94.18 (C^2), 127.48 (C_{Ar}), 129.31 (C_{Ar}), 132.12 (C_{Ar}), 134.67 (C_{Ar}). MS (EI): m/z (%) = 226 (M^+, 93).

*2.2.13. 5-Chloro-6-(phenylthio)-1,3-dioxepane (**17**)*

Method 1. Et_3N (0.6 ml, 4.3 mmol) and *p*-toluenesulfonyl chloride (TsCl) (0.81 g, 4.25 mmol) were added to a solution of dioxepane **3** (0.96 g, 4.25 mmol) in 20 ml of CH_2Cl_2. The reaction mixture was allowed to stay at 20°C for 24 hours. Then, the solvent was removed under vacuum, and the product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 9 : 1).

Yield 87% (0.9 g), colorless oil. ^{1}H NMR ($CDCl_3$), δ: 3.23–3.29 m (1H, H^6, $^3J(H^6\ H^5) = 5.5$ Hz, $^3J(H^6\ H^7{}_B) = 6.3$ Hz, $^3J(H^6\ H^7{}_A) = 2.7$ Hz, $^4J(H^6\ H^4{}_A) = -1.0$ Hz), 3.72 ddd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.5$ Hz, $^3J(H^4{}_A\ H^5) = 6.1$ Hz), 3.75 ddd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.4$ Hz), 3.83 dt (1H, H^5, $^3J(H^5\ H^4{}_B) = 2.2$ Hz), 4.08 dd (1H, $H^7{}_B$), 4.11 dd (1H, $H^4{}_B$), 4.62 and 4.65 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.4$ Hz), 7.12–7.35 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 55.71 (C^6), 60.67 (C^7), 65.34 (C^4), 66.89 (C^5), 93.93 (C^2), 127.76 (C_{Ar}), 129.28 (C_{Ar}), 132.16 (C_{Ar}), 133.01 (C_{Ar}). MS (EI): m/z (%) = 244 (M^+, 83), 245 (M^+, 12), 246 (M^+, 38).

Method 2. Et_3N (1.33 ml, 9.5 mmol) and methylsulfonyl chloride (MsCl) (1.15 g, 10 mmol) were added to a solution of dioxepane **3** (2.12 g, 9.4 mmol) in 20 ml of CH_2Cl_2. The reaction mixture was allowed to stay at 20°C for 24 hours. Then, the solvent was removed under vacuum, and the product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 9 : 1). Yield 76% (1.75 g), colorless oil.

Method 3. $SOCl_2$ (0.31 g, 2.6 mmol) was added to a solution of dioxepane **3** (0.3 g, 1.3 mmol) in 30 ml of $CHCl_3$. The mixture was allowed to stay at 20°C for 24 hours. Then, the solvent was removed by distillation under vacuum, and the product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 9 : 1). Yield 52% (0.17 g), colorless oil.

*2.2.14. 5-Methoxy-6-(phenylthio)-1,3-dioxepane (**18**).* CH_3OH (30 ml) and double molar excess of NaOH were added to dioxepane **3** (1.57 g, 6.42 mmol), and the reaction mixture was heated on an oil bath under reflux for 10 hours. The solvent was evaporated, and the product was extracted with diethyl ether (2 × 10 ml) from the residue. The extract was evaporated under vacuum, and the product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 9 : 1).

Yield 46% (0.7 g), colorless oil. ^{1}H NMR ($CDCl_3$), δ: 3.22 dt (1H, H^6, $^3J(H^6\ H^5) = 4.9$ Hz, $^3J(H^6\ H^7{}_A) = 5.2$ Hz, $^3J(H^6\ H^7{}_B) = 2.2$ Hz), 3.28–3.34 m (1H, H^5, $^3J(H^5\ H^4{}_A) = 5.9$ Hz, $^3J(H^5\ H^4{}_B) = 2.5$ Hz, $^4J(H^5\ H^7{}_A) = -1.1$ Hz), 3.34 s (3H, CH_3), 3.75–3.87 m (1H, $H^4{}_A$, $H^7{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.3$ Hz, $^2J(H^7{}_A\ H^7{}_B) = -12.6$ Hz), 3.96 dd (1H, $H^7{}_B$), 4.05 dd (1H, $H^4{}_B$), 4.69 and 4.73 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.45$ Hz), 7.17–7.44 m (5H, C_6H_5).^{13}C NMR ($CDCl_3$), δ: 52.41 (C^6), 57.43 (CH_3), 64.63 (C^7), 65.32 (C^4), 81.37 (C^5), 94.46 (C^2), 127.24 (C_{Ar}), 129.15 (C_{Ar}), 131.67 (C_{Ar}), 134.35 (C_{Ar}). MS (EI): m/z (%) = 240 (M^+, 86).

*2.2.15. 3,5-Dioxa-8-thiabicyclo[5.1.0]octane (**19**).* A mixture of epoxide **2** (1 g, 8.62 mmol), $CS(NH_2)_2$ (0.66 g, 8.62 mmol), 0.2 ml of concentrated H_2SO_4, and 2.5 ml of water was stirred for 10 minutes at 20°C. Then, the solution of 0.8 g of K_2CO_3 in 4 ml of water was added dropwise to the reaction mixture. The product was extracted with benzene (3 × 5 ml), and the extract was dried over $MgSO_4$. The solvent was removed on a rotary evaporator at 20°C. Yield 68% (0.77 g), colorless crystals. The spectral data for the obtained compound completely correspond to those reported in literature [28].

*2.2.16. 6-(Phenylthio)-1,3-dioxepan-5-thiol (**20**).* A mixture of thiophenol (0.45 g, 4.1 mmol), thiirane **19** (0.53 g, 4.02 mmol), and a catalytic amount of K_2CO_3 was heated until the appearance of first bubbles. The heating source was removed, and a short-time (<1 minute) spontaneous boiling-up with a sharp increase of the temperature was observed. The reaction mixture was cooled, and the product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 9 : 1).

Yield 62% (0.6 g), colorless oil. ^{1}H NMR ($CDCl_3$), δ: 2.02 d (1H, SH, $^3J(SH\ H^5) = 7.9$ Hz), 2.77–2.86 m (1H, H^5, $^3J(H^5\ H^6) = 6.4$ Hz, $^3J(H^5\ H^4{}_A) = 6.8$ Hz, $^3J(H^5\ H^4{}_B) = 2.8$ Hz, $^4J(H^5\ H^7{}_A) = -0.7$ Hz), 3.05 dt (1H, H^6, $^3J(H^6\ H^7{}_A) = 7.0$ Hz, $^3J(H^6\ H^7{}_B) = 2.8$ Hz, $^4J(H^6\ H^4{}_A) = -0.7$ Hz), 3.54 dd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.1$ Hz), 3.67 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.3$ Hz), 3.94 dd (1H, $H^7{}_B$), 3.99 dd (1H, $H^4{}_B$), 4.55 and 4.65 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.3$ Hz), 7.03–7.31 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 43.31 (C^5), 56.78 (C^6), 66.39 (C^7), 67.64 (C^4), 93.80 (C^2), 127.53 (C_{Ar}), 129.13 (C_{Ar}), 132.20 (C_{Ar}), 133.36 (C_{Ar}). MS (EI): m/z (%) = 242 (M^+, 5).

*2.2.17. 6-(Benzylthio)-1,3-dioxepan-5-ol (**21**).* Compound **21** was obtained from epoxide **2** (1.12 g, 9.66 mmol) using

a procedure similar to that used for the synthesis of compound **3**. NaOH was used instead of K_2CO_3.

Yield 71% (1.64 g), colorless oil. ^{1}H NMR ($CDCl_3$), δ: 2.68–2.73 m (1H, H^6, $^3J(H^6\ H^5) = 6.0$ Hz, $^3J(H^6\ H^7{}_A) = 6.7$ Hz, $^3J(H^6\ H^7{}_B) = 3.0$ Hz, $^4J(H^6\ H^4{}_A) = -0.9$ Hz), 2.78 br. s (1H, OH), 3.62 dt (1H, H^5, $^3J(H^5\ H^4{}_A) = 6.2$ Hz, $^3J(H^5\ H^4{}_B) = 2.1$ Hz), 3.67 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.4$ Hz), 3.70 ddd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -11.9$ Hz), 3.78 s (2H, CH_2S), 3.88 dd (1H, $H^7{}_B$), 4.00 dd (1H, $H^4{}_B$), 4.70 and 4.72 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.5$ Hz), 7.23–7.39 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 35.83 (CH_2S), 51.71 (C^6), 65.93 (C^7), 66.77 (C^4), 72.03 (C^5), 94.25 (C^2), 127.45 (C_{Ar}), 128.80 (C_{Ar}), 128.89 (C_{Ar}), 138.16 (C_{Ar}). MS (EI): m/z (%) = 240 (M^+, 51).

*2.2.18. 6-Phenoxy-1,3-dioxepan-5-ol (**22**).* Compound **22** was obtained from epoxide **2** (0.75 g, 6.47 mmol) using a procedure similar to that used for the synthesis of compound **3**.

Yield 81% (1.1 g), colorless oil. ^{1}H NMR ($CDCl_3$), δ: 3.30 br. d (1H, OH, $^3J(OH\ H^5) = 7.4$ Hz), 3.77 ddd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.3$ Hz, $^3J(H^6\ H^7{}_A) = 5.0$ Hz, $^4J(H^5\ H^7{}_A) = -0.8$ Hz), 3.87–3.96 m (3H, H^5, $H^4{}_A$ $H^4{}_B$), 4.03 dd (1H, $H^7{}_B$, $^3J(H^6\ H^7{}_B) = 1.8$ Hz), 4.31–4.35 m (1H, H^6), 4.77 and 4.80 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.7$ Hz), 6.94–7.32 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 64.50 (C^4), 65.53 (C^7), 70.97 (C^5), 78.94 (C^6), 94.59 (C^2), 115.96 (C_{Ar}), 121.61 (C_{Ar}), 129.68 (C_{Ar}), 157.07 (C_{Ar}). MS (EI): m/z (%) = 210 (M^+, 71).

*2.2.19. 6-(Phenylamino)-1,3-dioxepan-5-ol (**23**).* Compound **23** was obtained from epoxide **2** (0.36 g, 3.10 mmol) using a procedure similar to that used for the synthesis of compound **3**. NaOH was used instead of K_2CO_3.

Yield 29% (0.19 g), yellow oil. ^{1}H NMR ($CDCl_3$), δ: 2.80 br. s (1H, OH), 3.52–3.56 m (1H, H^6), 3.74–3.91 m (4H, H^5, $H^4{}_A$, $H^7{}_A$, $H^7{}_B$), 4.00 dd (1H, $H^4{}_B$, $^2J(H^4{}_A\ H^4{}_B) = -12.2$ Hz, $^4J(H^6\ H^4{}_B) = -1.5$ Hz), 4.31 br. s (1H, NH), 4.78 and 4.80 (AB, 2H, H^2, $^2J(H^2{}_A\ H^2{}_B) = -4.4$ Hz), 6.64–7.23 m (5H, C_6H_5). ^{13}C NMR ($CDCl_3$), δ: 56.98 (C^6), 64.41 (C^7), 65.57 (C^4), 69.98 (C^5), 94.20 (C^2), 113.04 (C_{Ar}), 117.73 (C_{Ar}), 129.63 (C_{Ar}), 146.12 (C_{Ar}). MS (EI): m/z (%) = 209 (M^+, 61).

*2.2.20. 6-(o-Tolylthio)-1,3-dioxepan-5-ol (**24**).* Epoxide **2** (0.2 g, 1.72 mmol) was added to a solution of *o*-toluenethiol (0.257 g, 2.07 mmol) and NaOH (0.083 g, 2.07 mmol) in 30 ml of methanol, and the reaction mixture was stirred at 50°C for 3 hours. The solvent was evaporated, and the product was extracted with diethyl ether (2 × 10 ml) from the residue. The extract was concentrated under vacuum, and the product was purified by column chromatography (eluent petroleum ether-ethyl acetate, 4 : 1).

Yield 85% (0.35 g), yellow oil. ^{1}H NMR ($CDCl_3$), δ: 2.43 s (1H, CH_3), 2.93 br. s (1H, OH), 3.21–3.25 m (1H, H^6, $^3J(H^6H^5) = 5.5$ Hz, $^3J(H^6H^7{}_A) = 5.8$ Hz, $^3J(H^6H^7{}_B) = 2.7$ Hz, $^4J(H^6H^4{}_A) = -0.9$ Hz), 3.72 dt (1H, H^5, $^3J(H^5H^4{}_A) = 5.7$ Hz, $^3J(H^5H^4{}_B) = 1.6$ Hz), 3.78 ddd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -11.9$ Hz), 3.87 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.5$ Hz), 4.04 dd (1H, $H^7{}_B$), 4.13 dd (1H, $H^4{}_B$), 4.76 and 4.77 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.9$ Hz), 7.13–7.44 m (4H, 2-$CH_3C_6H_4$). ^{13}C NMR ($CDCl_3$), δ: 20.90 (CH_3), 54.13 (C^6), 65.42 (C^7), 66.50 (C^4), 71.73 (C^5), 94.38 (C^2), 126.77 (C_{Ar}), 127.38 (C_{Ar}), 130.66 (C_{Ar}), 131.41 (C_{Ar}), 132.99 (C_{Ar}), 139.56 (C_{Ar}). MS (EI): m/z (%) = 240 (M^+, 39).

*2.2.21. 6-(p-Tolylthio)-1,3-dioxepan-5-ol (**25**).* Compound **25** was obtained from epoxide **2** (0.2 g, 1.72 mmol) using a procedure similar to that used for the synthesis of compound **24**.

Yield 88% (0.36 g), colorless crystals, m.p. 54–55°C. ^{1}H NMR ($CDCl_3$), δ: 2.33 s (1H, CH_3), 2.80 br. s (1H, OH), 3.10–3.14 m (1H, H^6, $^3J(H^6\ H^5) = 6.0$ Hz, $^3J(H^6\ H^7{}_A) = 6.7$ Hz, $^3J(H^6\ H^7{}_B) = 2.9$ Hz, $^4J(H^6\ H^4{}_A) = -0.7$ Hz), 3.66 dt (1H, H^5, $^3J(H^5\ H^4{}_A) = 6.2$ Hz, $^3J(H^5\ H^4{}_B) = 2.1$ Hz), 3.73 ddd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -11.8$ Hz), 3.79 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.4$ Hz), 4.04 dd (1H, $H^7{}_B$), 4.08 dd (1H, $H^4{}_B$), 4.72 and 4.75 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.5$ Hz), 7.09–7.37 m (4H, 4-$CH_3C_6H_4$). ^{13}C NMR ($CDCl_3$), δ: 21.19 (CH_3), 55.41 (C^6), 65.74 (C^7), 66.60 (C^4), 71.51 (C^5), 94.31 (C^2), 129.28 (C_{Ar}), 130.07 (C_{Ar}), 132.98 (C_{Ar}), 138.07 (C_{Ar}). MS (EI): m/z (%) = 240 (M^+, 51).

*2.2.22. 6-((2-Chlorophenyl)thio)-1,3-dioxepan-5-ol (**26**).* Compound **26** was obtained from epoxide **2** (0.2 g, 1.72 mmol) using a procedure similar to that used for the synthesis of compound **24**.

Yield 68% (0.31 g), yellow oil. ^{1}H NMR ($CDCl_3$), δ: 3.08 br. s (1H, OH), 3.28–3.32 m (1H, H^6, $^3J(H^6\ H^5) = 5.3$ Hz, $^3J(H^6\ H^7{}_A) = 5.7$ Hz, $^3J(H^6\ H^7{}_B) = 2.7$ Hz, $^4J(H^6\ H^4{}_A) = -1.1$ Hz), 3.68–3.74 br. m (1H, H^5, $^3J(H^5\ H^4{}_A) = 5.5$ Hz, $^3J(H^5\ H^4{}_B) = 1.7$ Hz), 3.77 ddd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.1$ Hz), 3.91 ddd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.6$ Hz, $^4J(H^7{}_A\ H^5) = -0.5$ Hz), 4.07 dd (1H, $H^7{}_B$), 4.13 dd (1H, $H^4{}_B$), 4.75 and 4.76 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.5$ Hz), 7.16–7.48 m (4H, 2-ClC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 53.85 (C^6), 65.23 (C^7), 66.49 (C^4), 71.57 (C^5), 94.39 (C^2), 127.46 (C_{Ar}), 128.51 (C_{Ar}), 130.28 (C_{Ar}), 132.50 (C_{Ar}), 132.97 (C_{Ar}), 136.23 (C_{Ar}). MS (EI): m/z (%) = 260 (M^+, 53), 262 (M^+, 24).

*2.2.23. 6-((4-Chlorophenyl)thio)-1,3-dioxepan-5-ol (**27**).* Compound **27** was obtained from epoxide **2** (0.2 g, 1.72 mmol) using a procedure similar to that used for the synthesis of compound **24**.

Yield 88% (0.4 g), colorless crystals, m.p. 67–68°C. ^{1}H NMR($CDCl_3$), δ: 2.79 dd (1H, OH, $^3J(OHH^5) = 6.8$ Hz, $^4J = -1.4$ Hz), 3.02–3.06 m (1H, H^6, $^3J(H^6H^5) = 5.7$ Hz, $^3J(H^6\ H^7{}_A) = 6.0$ Hz, $^3J(H^6\ H^7{}_B) = 2.7$ Hz), 3.50–3.55 br. m (1H, H^5, $^3J(H^5\ H^4{}_A) = 5.7$ Hz, $^3J(H^5\ H^4{}_B) = 1.8$ Hz), 3.61 ddd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.1$ Hz, $^4J(H^4{}_A\ H^6) = -0.8$ Hz), 3.69 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.6$ Hz), 3.90 dd (1H, $H^7{}_B$), 3.93 dd (1H, $H^4{}_B$), 4.59 and 4.61 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.5$ Hz), 7.10–7.24 m (4H, 4-ClC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 55.13 (C^6), 65.35 (C^7), 66.40 (C^4), 71.49 (C^5), 94.32 (C^2), 129.46 (C_{Ar}), 32.01 (C_{Ar}), 133.27 (C_{Ar}), 133.79 (C_{Ar}). MS (EI): m/z (%) = 260 (M^+, 61), 262 (M^+, 28).

*2.2.24. 6-((2,4-Dichlorophenyl)thio)-1,3-dioxepan-5-ol (**28**).* Compound **28** was obtained from epoxide **2** (0.2 g, 1.72 mmol) using a procedure similar to that used for the synthesis of compound **24**.

Yield 80% (0.40 g), colorless crystals, m.p. 70–71°C. ^{1}H NMR ($CDCl_3$), δ: 3.13 br. d (1H, OH, ^3J(OHH^5) = 5.6 Hz), 3.24–3.28 m (1H, H^6, ^3J(H^6 H$^7{}_A$) = 5.4 Hz, ^3J(H^6 H$^7{}_B$) = 2.6 Hz), 3.67–3.72 br. m (1H, H^5, ^3J(H^5 H$^4{}_A$) = 5.2 Hz, ^3J(H^5 H$^4{}_B$) = 1.7 Hz), 3.78 ddd (1H, H$^4{}_A$, ^2J(H$^4{}_A$ H$^4{}_B$) = −12.2 Hz, ^4J(H$^4{}_A$ H^6) = −1.1 Hz), 3.91 ddd (1H, H$^7{}_A$, ^2J(H$^7{}_A$ H$^7{}_B$) = −12.6 Hz, ^4J(H$^7{}_A$ H^5) = −0.7 Hz), 4.06 dd (1H, H$^7{}_B$), 4.12 dd (1H, H$^4{}_B$), 4.76 s (2H, 2H^2), 7.19–7.45 m (3H, 2,4-$Cl_2C_6H_3$). ^{13}C NMR ($CDCl_3$), δ: 54.11 (C^6), 65.07 (C^7), 66.34 (C^4), 71.51 (C^5), 94.40 (C^2), 127.77 (C_{Ar}), 129.05 (C_{Ar}), 130.13 (C_{Ar}), 131.71 (C_{Ar}), 133.37 (C_{Ar}), 133.96 (C_{Ar}), 137.11 (C_{Ar}). MS (EI): m/z (%) = 294 (M$^+$, 46), 296 (M$^+$, 22).

*2.2.25. 6-((2-Fluorophenyl)thio)-1,3-dioxepan-5-ol (**29**).* Compound **29** was obtained from epoxide **2** (0.2 g, 1.72 mmol) using a procedure similar to that used for the synthesis of compound **24**.

Yield 93% (0.39 g), colorless oil. ^{1}H NMR ($CDCl_3$), δ: 3.07 br. s (1H, OH), 3.15–3.19 m (1H, H^6, ^3J(H^6 H^5) = 5.4 Hz, ^3J(H^6 H$^7{}_A$) = 6.3 Hz, ^3J(H^6 H$^7{}_B$) = 2.8 Hz), 3.63–3.67 m (1H, H^5, ^3J(H^5 H$^4{}_A$) = 5.7 Hz, ^3J(H^5 H$^4{}_B$) = 1.8 Hz), 3.74 ddd (1H, H$^4{}_A$, ^2J(H$^4{}_A$ H$^4{}_B$) = −12.0 Hz), 3.83 dd (1H, H$^7{}_A$), 4.04 dd (1H, H$^7{}_A$, ^2J(H$^7{}_A$ H$^7{}_B$) = −12.5 Hz), 4.09 dd (1H, H$^4{}_B$), 4.72 and 4.74 (AB, 2H, ^2J(H$^2{}_A$ H$^2{}_B$) = −4.4 Hz), 7.04–7.51 m (4H, 2-FC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 54.61 (C^6, ^4J(FC^6) = −1.2 Hz), 65.41 (C^7), 66.44 (C^4), 71.63 (C^5), 94.20 (C^2), 116.20 (C_{Ar}, ^2J = −23.1 Hz), 120.02 (C_{Ar}, ^2J = −18.0 Hz), 124.75 (C_{Ar}, ^3J = 3.8 Hz), 130.38 (C_{Ar}, ^3J = 8.1 Hz), 135.49 (C_{Ar}), 162.59 (C_{Ar}, ^1J = 246.0 Hz). MALDI-MS: 267 $[M + Na]^+$, 283 $[M + K]^+$.

*2.2.26. 6-((4-Fluorophenyl)thio)-1,3-dioxepan-5-ol (**30**).* Compound **30** was obtained from epoxide **2** (0.2 g, 1.72 mmol) using a procedure similar to that used for the synthesis of compound **24**.

Yield 89% (0.37 g), colorless crystals, m.p. 86–87°C. ^{1}H NMR ($CDCl_3$), δ: 2.91 br. s (1H,OH), 3.08–3.12 m (1H, H^6, ^3J(H^6 H^5) = 5.9 Hz, ^3J(H^6 H$^7{}_A$) = 6.4 Hz, ^3J(H^6 H$^7{}_B$) = 2.8 Hz, ^4J(H^6 H$^4{}_A$) = −0.8 Hz), 3.63–3.68 br. m (1H, H^5, ^3J(H^5 H$^4{}_A$) = 6.0 Hz, ^3J(H^5 H$^4{}_B$) = 2.1 Hz), 3.74 ddd (1H, H$^4{}_A$, ^2J(H$^4{}_A$ H$^4{}_B$) = −12.0 Hz), 3.80 dd (1H,H$^7{}_A$, ^2J(H$^7{}_A$ H$^7{}_B$) = −12.5 Hz), 4.02dd (1H, H$^7{}_B$), 4.07 dd (1H, H$^4{}_B$), 4.72 and 4.74 (AB, 2H, ^2J(H$^2{}_A$ H$^2{}_B$) = −4.4 Hz), 9.97–7.48 m (4H, 4-FC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 55.89 (C^6), 65.47 (C^7), 66.47 (C^4), 71.44 (C^5), 94.31 (C^2), 116.46 (C_{Ar}, ^2J = −21.9 Hz), 128.19 (C_{Ar}), 135.14 (C_{Ar}, ^3J = 8.2 Hz), 162.76 (C_{Ar}, ^1J = 248.5 Hz). MALDI-MS: 267 $[M + Na]^+$, 283 $[M + K]^+$.

*2.2.27. 6-((2-Bromophenyl)thio)-1,3-dioxepan-5-ol (**31**).* Compound **31** was obtained from epoxide **2** (0.2 g, 1.72 mmol) using a procedure similar to that used for the synthesis of compound **24**.

Yield 78% (0.41 g), colorless oil. ^{1}H NMR ($CDCl_3$), δ: 3.01 br. s (1H, OH), 3.29–3.33 m (1H, H^6, ^3J(H^6 H^5) = 5.5 Hz, ^3J(H^6 H$^7{}_A$) = 5.7 Hz, ^3J(H^6 H$^7{}_B$) = 2.7 Hz, ^4J(H^6 H$^4{}_A$) = −1.2 Hz), 3.72 dt (1H, H^5, ^3J(H^5 H$^4{}_A$) = 5.3 Hz, ^3J(H^5 H$^4{}_B$) = 1.5 Hz), 3.78 ddd (1H, H$^4{}_A$, ^2J(H$^4{}_A$ H$^4{}_B$) = −12.1 Hz), 3.93 dd (1H, H$^7{}_A$, ^2J(H$^7{}_A$ H$^7{}_B$) = −12.6 Hz), 4.14 dd (1H, H$^7{}_B$), 4.14 dd (1H, H$^4{}_B$), 4.75 and 4.76 (AB, 2H, ^2J(H$^2{}_A$ H$^2{}_B$) = −4.6 Hz), 7.07–7.60 m (4H, 2-BrC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 54.17 (C^6), 65.21 (C^7), 66.51 (C^4), 71.51 (C^5), 94.42 (C^2), 126.70 (C_{Ar}), 128.12 (C_{Ar}), 128.50 (C_{Ar}), 132.03 (C_{Ar}), 133.59 (C_{Ar}), 135.14 (C_{Ar}). MALDI-MS: 328 $[M + Na]^+$, 344 $[M + K]^+$.

*2.2.28. 6-((3-Bromophenyl)thio)-1,3-dioxepan-5-ol (**32**).* Compound **32** was obtained from epoxide **2** (0.2 g, 1.72 mmol) using a procedure similar to that used for the synthesis of compound **24**.

Yield 89% (0.47 g), colorless oil. ^{1}H NMR ($CDCl_3$), δ: 2.96 br. s (1H, OH), 3.22–3.26 m (1H, H^6, ^3J(H^6 H^5) = 5.4 Hz, ^3J(H^6 H$^7{}_A$) = 5.8 Hz, ^3J(H^6 H$^7{}_B$) = 2.7 Hz), 3.69 dt (1H, H^5, ^3J(H^5 H$^4{}_A$) = 5.5 Hz, ^3J(H^5 H$^4{}_B$) = 1.5 Hz), 3.76 dd (1H, H$^4{}_A$, ^2J(H$^4{}_A$ H$^4{}_B$) = −12.0 Hz), 3.84 dd (1H, H$^7{}_A$, ^2J(H$^7{}_A$ H$^7{}_B$) = −12.5 Hz), 4.04 dd (1H, H$^7{}_B$), 4.06 dd (1H, H$^4{}_B$), 4.73 and 4.74 (1H, ^2J(H$^2{}_A$ H$^2{}_B$) = −4.6 Hz), 7.13–7.56 m (4H, 3-BrC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 54.75 (C^6), 65.22 (C^7), 66.39 (C^4), 71.50 (C^5), 94.27 (C^2), 122.98 (C_{Ar}), 129.86 (C_{Ar}), 130.44 (C_{Ar}), 130.53 (C_{Ar}), 133.86 (C_{Ar}), 136.13 (C_{Ar}). MALDI-MS: 328 $[M + Na]^+$, 344 $[M + K]^+$.

*2.2.29. 6-((4-Bromophenyl)thio)-1,3-dioxepan-5-ol (**33**).* Compound **33** was obtained from epoxide **2** (0.2 g, 1.72 mmol) using a procedure similar to that used for the synthesis of compound **24**.

Yield 91% (0.48 g), colorless crystals, m.p. 58–59°C. ^{1}H NMR ($CDCl_3$) δ: 3.00 br. d (1H, OH, ^3J(OH H^5) = 3.5 Hz), 3.18–3.23 m (1H, H^6, ^3J(H^6 H^5) = 5.5 Hz, ^3J(H^6 H$^7{}_A$) = 5.9 Hz, ^3J(H^6 H$^7{}_B$) = 2.7 Hz, ^4J(H^6 H$^4{}_A$) = −0.8 Hz), 3.72–3.77 br. m (1H, H^5, ^3J(H^5 H$^4{}_A$) = 5.7 Hz), 3.74–3.78 m (1H, H$^4{}_A$, ^2J(H$^4{}_A$ H$^4{}_B$) = −12.1 Hz), 3.83 dd (1H, H$^7{}_A$, ^2J(H$^7{}_A$ H$^7{}_B$) = −12.5 Hz), 4.05 t (1H, H$^7{}_B$), 4.06 t (1H, H$^4{}_B$), 4.73 and 4.75 (AB, 2H, ^2J (H$^2{}_A$ H$^2{}_B$) = −4.6 Hz), 7.27–7.44 m (4H, 4-BrC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 54.91 (C^6), 65.28 (C^7), 66.39 (C^4), 71.46 (C^5), 94.30 (C^2), 121.66 (C_{Ar}), 132.36 (C_{Ar}), 132.74 (C_{Ar}), 133.30 (C_{Ar}). MALDI-MS: 328 $[M + Na]^+$, 344 $[M + K]^+$.

2.2.30. The Separation of Racemic 6-(Phenylthio)-1,3-dioxepan-5-ol 3 to Enantiomers by Fermentative Acylation with Use of Lipase PS. A mixture of vinyl acetate (2.3 ml, 25 mmol) and lipase PS (0.5 g) immobilized on a diatomite was added to a solution of racemic 6-(phenylthio)-1,3-dioxepan-5-ol **3** (2.83 g, 12.52 mmol) in 30 ml of toluene. The reaction mixture was stirred at 20°C for 48 hours. Then, lipase was filtered off, the solvent was evaporated under reduced pressure, and the product was separated by column chromatography (eluent petroleum ether-ethyl acetate, 7 : 1).

*2.2.31. (5S,6S)-6-(Phenylthio)-1,3-dioxepan-5-ol (**3-SS**).* Yield 45% (1.42 g), $[\alpha]^{24}{}_D$ = 1.7° (c, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample.

*2.2.32. (5R,6R)-6-(Phenylthio)-1,3-dioxepan-5-yl Acetate (**5-RR**).* Yield 46% (1.55 g), $[\alpha]^{24}_D = -5.3^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample.

*2.2.33. (5R,6R)-6-(Phenylthio)-1,3-dioxepan-5-ol (**3-RR**).* K_2CO_3 (28 g, 9.3 mmol) was added to a solution of compound **5-RR** (0.83 g, 3.1 mmol) in 20 ml methanol. The mixture was stirred for 1 hour, then K_2CO_3 was filtered off, and the solvent was removed under vacuum. The product was purified by column chromatography (eluent petroleum ether–ethyl acetate, 1 : 1). Yield 84% (0.59 g), $[\alpha]^{24}_D = -1.7^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample.

*2.2.34. (5S,6S)-6-((2-Fluorophenyl)thio)-1,3-dioxepan-5-ol (**29-SS**).* This compound was obtained from racemic alcohol **29** (1.00 g, 4.09 mmol) using a procedure similar to that used for the synthesis of compound **3-SS**. Yield 45% (0.45 g), colorless oil, $[\alpha]^{24}_D = 1.2^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample.

*2.2.35. (5R,6R)-6-((2-Fluorophenyl)thio)-1,3-dioxepan-5-yl Acetate (**34**).* This compound was obtained from racemic alcohol **29** (1.00 g, 4.09 mmol) using a procedure similar to that used for the synthesis of compound **5-RR**.

Yield 46% (0.54 g), colorless crystals, m.p. 51–52°C, $[\alpha]^{24}_D = -0.4^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. ^{1}H NMR ($CDCl_3$), δ: 2.05 s (3H, CH_3), 3.34–3.38 m (1H, H^6, $^3J(H^6\ H^5)$ = 5.5 Hz, $^3J(H^6\ H^7{}_A) = 6.5$ Hz, $^3J(H^6\ H^7{}_B) = 2.1$ Hz), 3.87 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.3$ Hz), 3.89 dd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.7$ Hz, $^3J(H^4{}_A\ H^5) = 5.6$ Hz), 4.08 dd (1H, $H^4{}_B$, $^3J(H^4{}_B\ H^5) = 2.1$ Hz), 4.15 ddd (1H, $H^7{}_B$), 4.75 and 4.80 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.4$ Hz), 4.87 dt (1H, H^5), 7.08–7.54 m (4H, 2-FC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 21.15 (CH_3), 51.89 (C^6), 65.23 ($C^{7(4)}$), 65.34 ($C^{4(7)}$), 73.82 (C^5), 94.49 (C^2), 116.18 (C_{Ar}, $^2J = -23.1$ Hz), 120.09 (C_{Ar}, $^2J = -17.8$ Hz), 124.76 (C_{Ar}, $^3J = 3.7$ Hz), 130.49 (C_{Ar}, $^3J = 8.0$ Hz), 135.60 (C_{Ar}), 162.69 (C_{Ar}, $^1J = 246.4$ Hz), 170.19 (CO). MALDI-MS: 309 $[M + Na]^+$, 328 $[M + K]^+$.

*2.2.36. (5R,6R)-6-((2-Fluorophenyl)thio)-1,3-dioxepan-5-ol (**29-RR**).* This compound was obtained from acetate **34** (0.5 g, 1.75 mmol) using a procedure similar to that used for the synthesis of compound **3-RR**. Yield 93% (0.40 g), colorless oil, $[\alpha]^{24}_D = -1.2^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample.

*2.2.37. (5S,6S)-6-((2-Bromophenyl)thio)-1,3-dioxepan-5-ol (**31-SS**).* This compound was obtained from racemic alcohol **31** (1.0 g, 3.28 mmol) using a procedure similar to that used for the synthesis of compound **3-SS**. Yield 41% (0.41 g), colorless oil, $[\alpha]^{24}_D = 1.0^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample.

*2.2.38. (5R,6R)-6-((2-Bromophenyl)thio)-1,3-dioxepan-5-yl Acetate (**35**).* This compound was obtained from racemic alcohol **31** (1 g, 3.28 mmol) using a procedure similar to that used for the synthesis of compound **5-RR**.

Yield 45% (0.51 g), colorless oil, $[\alpha]^{24}_D = -0.2^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. ^{1}H NMR ($CDCl_3$), δ: 2.08 s (3H, CH_3), 3.43–3.48 m (1H, H^6, $^3J(H^6\ H^5) = 4.6$ Hz, $^3J(H^6\ H^7{}_A) = 5.3$ Hz, $^3J(H^6\ H^7{}_B) = 2.2$ Hz, $^4J(H^6\ H^4{}_A) = -1.2$ Hz), 3.92 ddd (1H, H^4, $^2J(H^4{}_A\ H^4{}_B) = -12.8$ Hz, $^3J(H^4{}_A\ H^5) = 4.7$ Hz), 3.96 ddd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.3$ Hz, $^4J(H^7{}_A\ H^5) = -0.8$ Hz), 4.13 dd (1H, $H^4{}_B$, $^3J(H^4{}_B\ H^5) = 2.0$ Hz), 4.18 dd (1H, $H^7{}_B$), 4.77 and 4.82 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.4$ Hz), 4.92 dt (1H, H^5), 7.09–7.60 m (4H, 2–BrC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 21.13 (CH_3), 51.72 (C^6), 64.87 ($C^{7(4)}$), 65.47 ($C^{4(7)}$), 73.65 (C^5), 94.47 (C^2), 126.64 (C_{Ar}), 128.05 (C_{Ar}), 128.55 (C_{Ar}), 132.40 (C_{Ar}), 133.49 (C_{Ar}), 134.97 (C_{Ar}), 170.10 (CO). MALDI-MS: 370 $[M + Na]^+$, 386 $[M + K]^+$.

*2.2.39. (5R,6R)-6-((2-Bromophenyl)thio)-1,3-dioxepan-5-ol (**31-RR**).* This compound was obtained from acetate **35** (0.5 g, 1.44 mmol) using a procedure similar to that used for the synthesis of compound **3-RR**. Yield 98% (0.43 g), colorless oil, $[\alpha]^{24}_D = -1.0^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample.

*2.2.40. (5S,6S)-6-((3-Bromophenyl)thio)-1,3-dioxepan-5-ol (**32-SS**).* This compound was obtained from racemic alcohol **32** (1.0 g, 3.28 mmol) using a procedure similar to that used for the synthesis of compound **3-SS**. Yield 40% (0.40 g), colorless crystals, m.p. 69–70°C, $[\alpha]^{24}_D = 1.2^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample. HPLC retention time 109.9 min (chiral stationary phase).

*2.2.41. (5R,6R)-6-((3-Bromophenyl)thio)-1,3-dioxepan-5-yl Acetate (**36**).* This compound was obtained from racemic alcohol **32** (1.0 g, 3.28 mmol) using a procedure similar to that used for the synthesis of compound **5-RR**.

Yield 40% (0.45 g), colorless oil, $[\alpha]^{24}_D = -0.1^\circ$ (*c*, 5; CH_2Cl_2), ee > 99%. ^{1}H NMR ($CDCl_3$), δ: 2.09 s (3H, CH_3), 3.45 dt (1H, H^6, $^3J(H^6\ H^5) = 5.4$ Hz, $^3J(H^6\ H^7{}_A) = 6.2$ Hz, $^3J(H^6\ H^7{}_B) = 2.3$ Hz), 3.84 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.3$ Hz), 3.87 dd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.3$ Hz, $^3J(H^4{}_A\ H^5) = 5.4$ Hz), 4.03 dd (1H, $H^4{}_B$, $^3J(H^4{}_B\ H^5) = 2.3$ Hz), 4.13 dd (1H, $H^7{}_B$), 4.74 and 4.80 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.6$ Hz), 4.92 dt (1H, H^5), 7.15–7.63 m (4H, 3-BrC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 21.07 (CH_3), 52.06 (C^6), 65.08 ($C^{7(4)}$), 65.40 ($C^{4(7)}$), 73.65 (C^5), 94.38 (C^2), 122.84 (C_{Ar}), 129.85 (C_{Ar}), 130.37 (C_{Ar}), 130.42 (C_{Ar}), 133.81 (C_{Ar}), 136.07 (C_{Ar}), 170.04 (CO). MALDI-MS: 370 $[M + Na]^+$, 386 $[M + K]^+$.

*2.2.42. (5R,6R)-6-((3-Bromophenyl)thio)-1,3-dioxepan-5-ol (**32-RR**).* This compound was obtained from acetate **36** (0.5 g, 1.44 mmol) using a procedure similar to that used for the synthesis of compound **3-RR**. Yield 98% (0.43 g), colorless crystals, m.p. 69–70°C, $[\alpha]^{24}_D = -1.2^\circ$ (*c*, 5; CH_2Cl_2),

ee > 99%. The spectral data completely correspond to the racemic sample. HPLC retention time 116.6 min (chiral stationary phase).

*2.2.43. (5S,6S)-6-((4-Bromophenyl)thio)-1,3-dioxepan-5-ol (**33-SS**).* This compound was obtained from racemic alcohol **33** (1.0 g, 3.28 mmol) using a procedure similar to that used for the synthesis of compound **3-SS**. Yield 39% (0.39 g), colorless crystals, m.p. 68–69°C, $[\alpha]^{24}_{D} = 1.0^{\circ}$ (*c*, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample.

*2.2.44. (5R,6R)-6-((4-Bromophenyl)thio)-1,3-dioxepan-5-yl Acetate (**37**).* This compound was obtained from racemic alcohol **33** (1.0 g, 3.28 mmol) using a procedure similar to that used for the synthesis of compound **5-RR**. Yield 40% (0.46 g), colorless oil, $[\alpha]^{24}_{D} = -0.9^{\circ}$ (*c*, 5; CH_2Cl_2), ee > 99%. ^{1}H NMR ($CDCl_3$), δ: 2.09 s (3H, CH_3), 3.32 dt (1H, H^6, $^3J(H^6\ H^5) = 5.4$ Hz, $^3J(H^6\ H^7{}_A) = 6.1$ Hz, $^3J(H^6\ H^7{}_B) = 2.4$ Hz), 3.82 dd (1H, $H^7{}_A$, $^2J(H^7{}_A\ H^7{}_B) = -12.3$ Hz), 3.86 dd (1H, $H^4{}_A$, $^2J(H^4{}_A\ H^4{}_B) = -12.5$ Hz, $^3J(H^4{}_A\ H^5) = 5.3$ Hz), 4.03 dd (1H, $H^4{}_B$, $^3J(H^4{}_B\ H^5) = 2.3$ Hz), 4.13 dd (1H, $H^7{}_B$), 4.73 and 4.80 (AB, 2H, $2H^2$, $^2J(H^2{}_A\ H^2{}_B) = -4.6$ Hz), 4.91 dt (1H, H^5), 7.32–7.44 m (4H, 4-BrC_6H_4). ^{13}C NMR ($CDCl_3$), δ: 21.13 (CH_3), 52.26 (C^6), 65.23 ($C^{7(4)}$), 65.45 ($C^{4(7)}$), 73.66 (C^5), 94.46 (C^2), 121.75 (C_{Ar}), 132.27 (C_{Ar}), 132.68 (C_{Ar}), 133.48 (C_{Ar}), 170.11 (CO). MALDI-MS: 370 $[M + Na]^+$, 386 $[M + K]^+$.

*2.2.45. (5R,6R)-6-((4-Bromophenyl)thio)-1,3-dioxepan-5-ol (**33-RR**).* This compound was obtained from racemic acetate **37** (0.5 g, 1.44 mmol) using a procedure similar to that used for the synthesis of compound **3-RR**. Yield 91% (0.40 g), colorless crystals, m.p. 68–69°C, $[\alpha]^{24}_{D} = -1.0^{\circ}$ (*c*, 5; CH_2Cl_2), ee > 99%. The spectral data completely correspond to the racemic sample.

2.3. Crystal Structure Determinations

The X-ray diffraction data for the crystals of **6**, **7**, and **9** were collected on a Smart Apex II automatic diffractometer using graphite monochromated radiation MoK_α (λ 0.71073). The structures were solved by a direct method using the SHELXS [21] program and refined by full-matrix least-squares using SHELXL2014 [21] program. All the nonhydrogen atoms were refined with anisotropic atomic displacement parameters. H(C) atoms were constrained as riding atoms, with the C–H set to 0.95 Å. All calculations were performed using WinGX [22] and APEX [23] programs. Crystallographic data (excluding structure factors) for the structures **6**, **7**, and **9** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication, the corresponding CCDC numbers are given in Table 1. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

2.4. Biological Studies

2.4.1. Antifungal Activity Studies. The antifungal activity has been tested against 4 clinical strains, *C. albicans*, *A. fumigatus*, *E. floccosum*, and *Mucor pusilos*, that were obtained from a collection of typical and clinical cultures of the mycological laboratory of the Kazan Research Institute of Epidemiology and Microbiology.

The fungal activity was evaluated *in vitro* using a minimum inhibitory concentration (MIC) test according to NCCLS guidelines. The tested substances were dissolved in Sabouraud medium to obtain the solutions with concentrations two times higher than the final ones. Then, 1 ml of each solution and 1 ml of fungal spore suspension (concentration of 10^6 fungal spores per 1 ml) were added to the test tube. The final concentrations of the tested compounds were (mg/ml): 10; 5; 2.5; 1.2; 0.6; 0.3; 0.15; 0.07; 0.03; 0.015; and 0.007. The fungal spore solutions or vegetative cells were obtained from a viable 48-hour old yeast-like fungal culture and 6-day old mycelial fungi. The test tubes were incubated at 28°C–30°C for 9 days. The culture growth was followed with a photoelectric colorimeter at 530 nm using pure medium as a blank control.

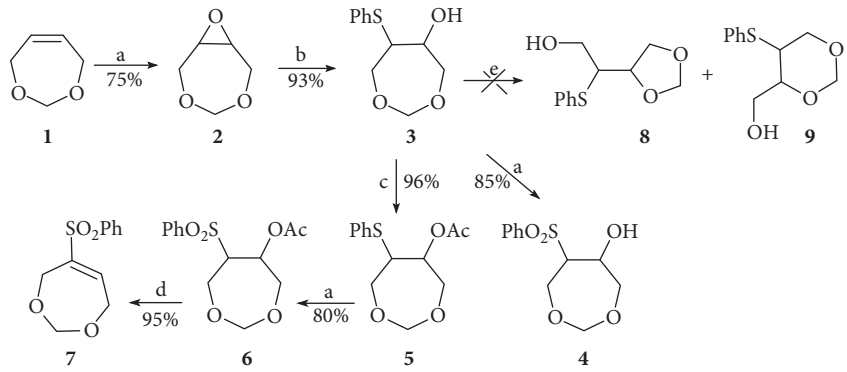
2.4.2. Cytotoxicity Studies. Human skin fibroblasts (HSFs) were isolated from the skin explant according to the conventional protocol [24]. HSFs cells were cultured in the minimum essential medium Eagle (a-MEM) supplemented with 10% fetal bovine serum, 2 mM L-glutamine, 100 μg/mL streptomycin, and 100 U/mL penicillin under standard conditions (37°C, 5% CO_2 atmosphere). Adhered cells were collected from the culture flask by detaching them with trypsin-EDTA solution. Suspended cells were by centrifugation at 200*g* in PBS. Cytotoxic concentrations (IC_{50}) of compounds were determined with the use of MTT assay. Cells were preseeded in a 96-well plate at the density of 1,000–2,000 cells per well and then incubated with aqueous solutions of the tested compounds for 3 days under standard conditions. Culture medium in the plate was then replaced by the fresh one supplemented with 0.5 mg/mL MTT and additionally kept for 4 h to allow for reduction of MTT into colored product (formazan) by metabolically active cells. Optical absorbance of produced formazan, proportional to viable cell number, was registered on an Infinite 200 PRO analyzer at 550 nm.

3. Results and Discussion

In continuation of our research on reactions of 3,5,8-trioxabicyclo[5.1.0]octanes with nucleophiles and antimycotic properties of the obtained products [13], in this work we have carried out the thiolysis reaction of epoxide **2** by thiophenol followed by functionalization of the resulting β-hydroxysulfide **3** (Scheme 1). The functionalization was performed by oxidation of the sulfur atom and/or acylation of the hydroxyl group (compounds **4**–**6**). Our attempts to synthesize compound **4** from acetate **6** by removing the acetate group with potassium carbonate led to formation of

Table 1: Parameters of crystals of compounds **6**, **7**, and **9** and conditions of X-ray diffraction experiments.

Compound reference	**6**	**7**	**9**
Temperature (K)	293 (2)	293 (2)	293 (2)
Chemical formula	$C_{13}H_{16}O_6S$	$C_{11}H_{12}O_4S$	$C_{11}H_{14}O_3S$
Formula mass	300.32	240.27	226.28
Crystal system	Triclinic	Monoclinic	Monoclinic
A (Å)	8.2534 (12)	12.770 (5)	17.337 (6)
b (Å)	9.2870 (14)	7.578 (3)	4.8550 (16)
c (Å)	10.2792 (15)	11.525 (5)	13.336 (4)
α (°)	110.116 (2)	90	90
β (°)	97.389 (2)	100.639 (5)	96.440 (3)
γ (°)	105.359 (2)	90	90
Unit cell volume (Å^3)	692.09 (18)	1096.1 (8)	1115.4 (6)
Space group	P-1	P21/c	P21/c
No. of formula units per unit cell (Z)	2	4	4
No. of reflections measured	3436	6931	8394
No. of independent reflections	1883	1764	2414
R_{int}	0.109	0.030	0.031
Final R_1 values ($I > 2\sigma(I)$)	0.0664	0.0351	0.0546
Final wR (F^2) values ($I > 2\sigma(I)$)	0.1807	0.0902	0.1462
Final R_1 values (all data)	0.0704	0.0426	0.0670
Final wR (F^2) values (all data)	0.1858	0.0949	0.1568
CCDC numbers	1513085	1513086	1513087



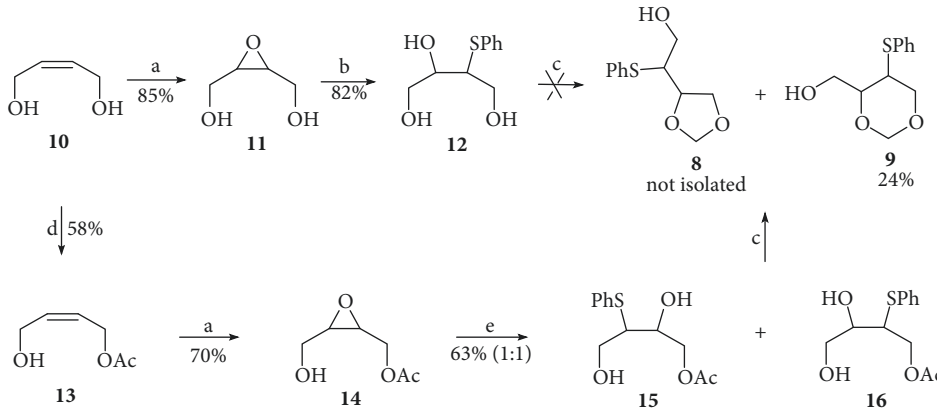
a - oxone, $(CH_3)_2CO$, $NaHCO_3$, H_2O, r.t.; **b** - PhSH, K_2CO_3, t°C; **c** - $(CH_3C(O))_2O$, Et_3N, CH_2Cl_2, r.t.; **d** - K_2CO_3, MeOH, 50°C; **e** - $PhCH_3$, TsOH, reflux, 10 h

Scheme 1: Synthesis of hydroxysulfide of 1,3-dioxepane series and its further functionalization.

compound **7**. This result suggested that the presence of the electron-withdrawing $PhSO_2$ fragment increased the acidity of methine proton which led to its elimination even under weak alkali treatment. Our further attempts to obtain the corresponding 1,3-dioxolane **8** and 1,3-dioxane **9** with the reduced cycle size via acidic isomerization of compound **3** were not successful.

In order to obtain compounds **8** and **9**, we then tried alternative synthetic routes depicted in Scheme 2. The intermediate **12** was obtained from diol **10** via its oxidation with oxone followed by thiolysis of the resulting epoxide **11** with thiophenol in hot water in the presence of DABCO. Further condensation of triol **12** with paraformaldehyde resulted in an inseparable mixture of compounds **3**, **8**, and **9**, as well as the products of their reaction with paraformaldehyde. ^{1}H NMR spectral data demonstrated that initial 1,3-dioxepane **3** was the major component of the reaction mixture in all cases. Similar results were described in a previous paper [25]. The condensation reaction of butane-1,2,4-triol with paraformaldehyde under similar conditions led to a mixture of five- and six-membered rings, where six-membered ring structure was the product of both kinetic and thermodynamic control [26, 27]. It was clear that the presence of thiophenyl group in triol **12** significantly changed the ratio of the obtained isomers. In general, the obtained results suggested that this method was unsuitable for the synthesis of **8** and **9**.

To evaluate the relative stability of the isomeric five-, six-, and seven-membered formals, we calculated the free energies for their structures by DFT quantum-chemical B3LYP/6-31G (d,p) method, which was previously validated for solution of the similar task for stereoisomers of



a - oxone, $(CH_3)_2CO$, $NaHCO_3$, H_2O, r.t.; **b** - PhSH, DABCO, H_2O, 90°C; **c** - $(CH_2O)n$, TsOH, CH_2Cl_2, r.t.; **d** - $(CH_3C(O))_2O$, Et_3N, CH_2Cl_2, r.t.; **e** - PhSH, K_2CO_3, t°C

Scheme 2: Synthesis of hydroxysulfides of 1,3-dioxane and 1,3-dioxolane series.

oxirane **2** and related compounds [28, 29]. These calculations aimed at determination of relative thermodynamic stability of cyclic acetals of different types–dioxepanes, dioxanes, and dioxolanes. It was found that dioxolane **8** and dioxane **9** were less stable than dioxepane **3**. The differences in the relative values of free energies for the mentioned rings ($\Delta\Delta G_{298}$ for the most stable conformers: 0.00 kcal/mol–dioxepan, 0.12 kcal/mol–dioxolane, and 0.69 kcal/mol–dioxane) allowed us to evaluate the expected "thermodynamic" ratio of products in the gas phase as 56:38:6. Accounting of solvation effects and possible involvement of other conformers of each cyclic isomer, as well as calculations using a different basis, could slightly change this ratio, but the same trend was observed. Thus, the replacement of proton on thiophenyl group in the third position of butane-1,2,4-triol led to preferential formation of the seven-membered cyclic product in the reaction of condensation of this triol with paraformaldehyde. It can be concluded that formation of the seven-membered ring is advantageous both in terms of thermodynamic (calculated data) and kinetic (experimental data for the condensation reaction) control.

Compound **9** was obtained using a series of reactions depicted in Scheme 2. At the first step, reaction of diol **10** with acetic anhydride (0.8 mol. equiv.) resulted in monoacetylated derivative **13**. According to ^{1}H NMR spectral data, the ratio of mono- and diacetylated products in unseparated mixture was 3 : 1. The analytical data for the obtained monoacetate **13** completely corresponded to those described in literature [19]. Compound **13** was then oxidized by oxone to previously described epoxide **14** [20]. Treatment of compound **14** with thiophenol in the presence of K_2CO_3 led to a mixture of regioisomers **15** and **16**. The reaction was strongly exothermic, with the temperature increase up to 150°C that could explain the lack of the reaction selectivity. The resulting mixture of acetates **15** and **16** was purified from initial thiophenol and triol **12**, formed in small amounts, by column chromatography on silica gel. The resulting acetates **15** and **16**, which could not be separated, were treated with paraformaldehyde to obtain the corresponding mixture of compounds **8** and **9**. Dioxane **9** was isolated by column chromatography on silica gel in 24% yield as white crystals. Its structure was confirmed by X-ray analysis (Figure 1). Dioxolane **8** could not be isolated in an individual form due to presence of impurities with close chromatographic mobility.

Our further synthetic effort was focused on structural modifications of compound **3**, including their enantiomerically enriched forms (Scheme 3). Treatment of alcohol **3** with *para*-toluenesulfonyl chloride or methanesulfonyl chloride in the presence of triethylamine (path a) resulted in formation of chloride **17** in 87% and 76% yields, respectively. The reaction with thionyl chloride (path b) was less successful and led to the desired product in 52% yield. Methyl ester **18** was prepared by reaction of chloride **17** in boiling methanol in the presence of an excess of sodium hydroxide.

The treatment of epoxide **2** with thiourea under aqueous acidic conditions led to episulfide **19**. The latter was treated with thiophenol in the presence of potassium carbonate without a solvent to obtain mercaptan **20** [28]. In addition, reactions of epoxide **2** with various nucleophiles, including benzylthiol, phenol, aniline, and halogen-substituted thiophenols, resulted in a series of congeneric alcohols **21**–**33**.

Structures of all the synthesized compounds were confirmed by 1D and 2D NMR spectroscopy, mass spectroscopy, and X-ray analysis. X-ray structures of compounds **6**, **7**, and **9** are shown in Figure 1.

At the next stage, several racemic compounds were separated into enantiomers using enzymatic acylation by lipase PS (Scheme 4) [18]. As a result of two-step synthesis, we obtained optically active alcohols **3**, **29**, **31**, **32**, and **33**, which had equal but opposite values of the rotation angles. Configuration of the chiral carbon atom at the hydroxyl group was assigned using the stereospecificity profile of reactions in the presence of lipase PS, in which only hydroxyl groups with R-configuration at the chiral center were prone to acylation. It was observed that the enzymatic reaction rate and optical purity of the resulting products did not depend on the nature and position of the halogen substituent in the aromatic rings of the studied thiophenyl moieties.

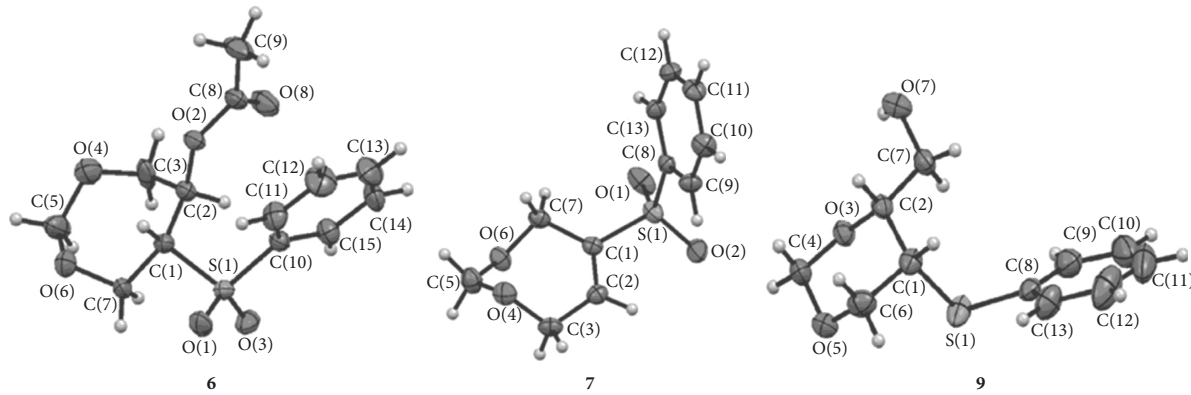
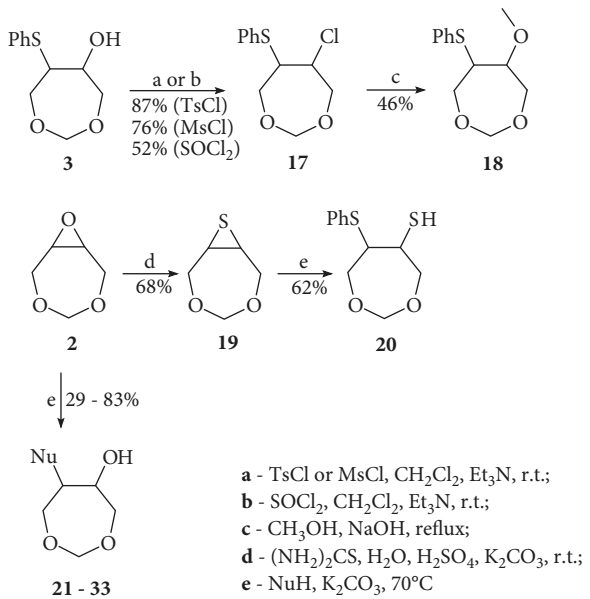


Figure 1: The geometry of compounds **6**, **7**, and **9** according to X-ray structural analysis.



Scheme 3: Synthesis of new functional derivatives of 1,3-dioxepane series.

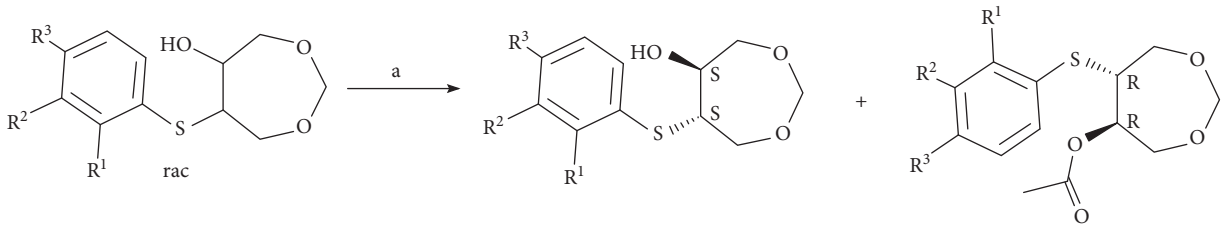
To confirm the enantiomeric purity of the obtained alcohols, NMR spectra were obtained in the presence of a shift reagent, europium(III) *tris*[3-(heptafluoropropylhydroxymethylene)-(+)-camphorate. Figure 2 shows fragments of ^{1}H NMR spectra of the studied samples in the region of signals of hydrogen atoms at the acetal carbon atom. For the optically active alcohols, there are no signals of the second enantiomer, and these data suggest that the enantiomeric excess is close to 100%. It should also be noted that a mismatch in the chemical shifts of the signals for each enantiomer with respect to racemate is explained by different amounts of the sample compounds loaded into a vial and the shift reagent. This factor also affects the shape and intensity of signals. The high enantiomeric purity (ee > 99%) of the leading compound **32-SS** was also confirmed by HPLC analysis on a chiral stationary phase.

At the final stage of the work, the antimycotic activity of the synthesized compounds against a panel of pathogenic microscopic fungi was tested. Specifically, we used four aggressive clinical isolates of fungi belonging to *C. albicans*, *A. fumigatus*, *E. floccosum*, and *M. pusillus* species. The *in vitro* experiment was carried out in liquid medium (Sabouraud glucose broth) using 2-fold serial dilutions in biological test tubes. Assessment of the culture growth was performed visually by comparing the growth of microorganisms in the presence of the studied test compounds and without them. The first lowest concentration of the tested sample (from a series of serial dilutions), where fungi growth was not visually detected, was considered as the minimum inhibitory concentration (MIC). As the reference compounds, two antimycotics with a broad spectrum of activity frequently used in clinical practice, fluconazole and terbinafine, were used.

The data presented in Table 2 indicate that several compounds had an expressed antifungal activity with MICs in the range of 15–60 μg/ml. Thus, the leading compound **32** in the form of a dextrorotatory SS-enantiomer inhibited the growth of the studied fungi at the level of terbinafine, one of the most powerful systemic antimycotics. Fluconazole was significantly less active in this experimental series. To assess potential therapeutic window, we have measured the cytotoxic activity of the obtained compounds against the normal cells, human adipose tissue fibroblasts. The presented experimental data (Table 2) indicate that the leading compound **32-SS** possesses a remarkable selectivity of action against the studied fungal pathogens (selectivity index is 5–10) as compared to terbinafine (selectivity index is 0.6–2 against the studied pathogens).

4. Conclusions

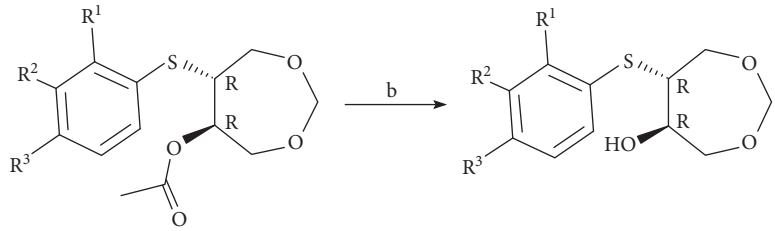
In conclusion, in this work, we have developed efficient synthetic approaches to a series of novel 6-(arylthio)-1,3-dioxepan-5-ols starting from 1,3-dioxacyclohept-5-ene through its oxidation followed by thiolysis with various thiophenols. Depending on the reaction conditions, this process can theoretically lead to the corresponding isomeric



(3) $R^1 = R^2 = R^3 = H$
(29) $R^1 = F, R^2 = R^3 = H$
(31) $R^1 = Br, R^2 = R^3 = H$
(32) $R^2 = Br, R^1 = R^3 = H$
(33) $R^3 = Br, R^1 = R^2 = H$

(3) $R^1 = R^2 = R^3 = H$
(29) $R^1 = F, R^2 = R^3 = H$
(31) $R^1 = Br, R^2 = R^3 = H$
(32) $R^2 = Br, R^1 = R^3 = H$
(33) $R^3 = Br, R^1 = R^2 = H$

(5) $R^1 = R^2 = R^3 = H$
(34) $R^1 = F, R^2 = R^3 = H$
(35) $R^1 = Br, R^2 = R^3 = H$
(36) $R^2 = Br, R^1 = R^3 = H$
(37) $R^3 = Br, R^1 = R^2 = H$



(5) $R^1 = R^2 = R^3 = H$
(34) $R^1 = F, R^2 = R^3 = H$
(35) $R^1 = Br, R^2 = R^3 = H$
(36) $R^2 = Br, R^1 = R^3 = H$
(37) $R^3 = Br, R^1 = R^2 = H$

(3) $R^1 = R^2 = R^3 = H$
(29) $R^1 = F, R^2 = R^3 = H$
(31) $R^1 = Br, R^2 = R^3 = H$
(32) $R^2 = Br, R^1 = R^3 = H$
(33) $R^3 = Br, R^1 = R^2 = H$

a - Lypase PS, 30–40°C, $PhCH_3$, vinylacetate; **b** - MeOH, K_2CO_3, r.t.

Scheme 4: Separation of racemic hydroxysulfides into enantiomers.

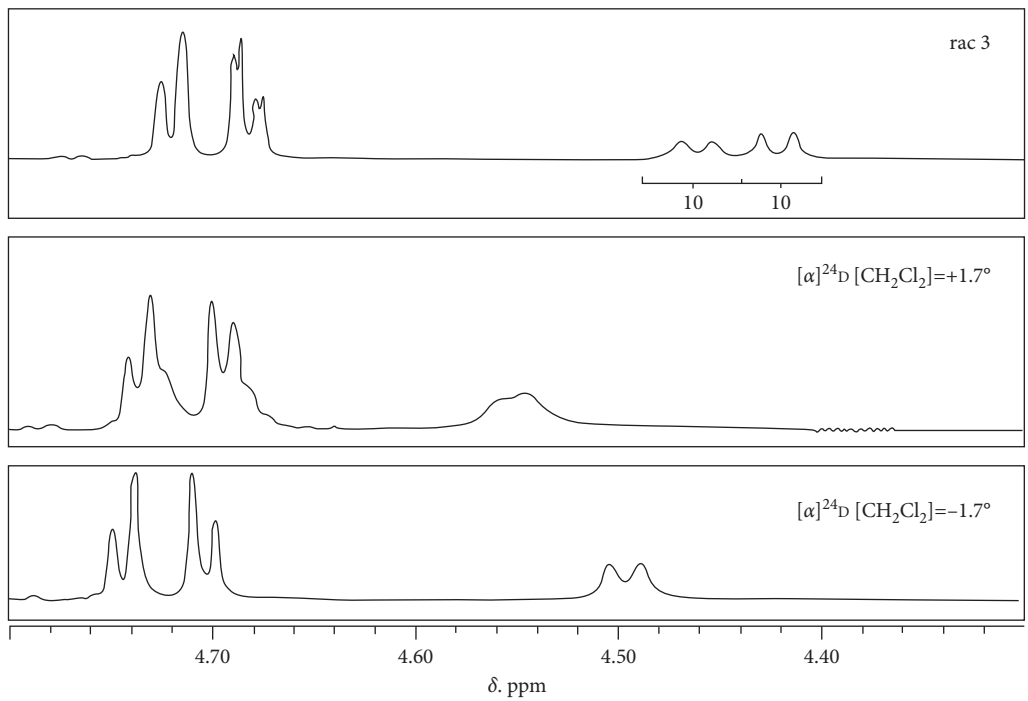


Figure 2: Fragments of 1H NMR spectra of racemic alcohol 3 and its enantiomers in the presence of a shift reagent.

Table 2: Minimum inhibitory concentrations (μg/ml) of the synthesized compounds against the studied fungal strains.

Compound	*Candida albicans*	*Aspergillus fumigatus*	*Epidermophyton floccosum*	*Mucor pusilos*	IC_{50} (μg/ml), human adipose tissue fibroblasts
3-SS	120	250	250	120	171.6 ± 5.8
3-RR	250	500	500	250	81.9 ± 2.2
3	250	500	500	250	n/a
21	>500	>500	>500	>500	n/a
22	60	120	>500	120	92.2 ± 8.7
23	>500	>500	>500	>500	n/a
24	120	120	120	120	202.2 ± 10.1
25	120	120	120	120	248.8 ± 12.5
26	120	120	500	250	142.2 ± 12.9
27	500	500	>500	250	135.5 ± 16.4
28	>500	>500	>500	>500	n/a
30	>500	>500	>500	>500	n/a
29-SS	120	120	120	120	364.5 ± 23.6
29-RR	250	250	250	250	500.6 ± 16.1
29	250	250	250	250	390.1 ± 20.1
31-SS	60	60	120	120	166.6 ± 12.8
31-RR	60	120	120	120	141.4 ± 14.5
31	120	120	120	120	143.3 ± 10.2
32-SS	15	15	15	30	156.0 ± 5.2
32-RR	60	60	60	120	178.3 ± 11.5
32	60	60	60	120	160.0 ± 4.1
33-SS	120	120	120	30	99.8 ± 2.9
33-RR	120	250	250	120	76.4 ± 4.8
33	120	250	250	120	80.9 ± 1.7
Fluconazole	120	250	250	250	>1500
Terbinafine	15	15	15	50	29.2 ± 3.4

five-, six-, and seven-membered cyclic acetals: 1,3-dioxolanes, 1,3-dioxanes, and 1,3-dioxepanes, respectively. However, our experimental data supported by quantum-chemical calculations using B3LYP/6-31G (d,p) method demonstrated that cyclic formals of 1,3-dioxepane series are the major products of this reaction. For such structures, the isomerization reaction is impossible due to instability of the intermediate carbocation. We have demonstrated that the corresponding 1,3-dioxolanes and 1,3-dioxanes can be obtained via alternative synthetic route based on condensation of monoacetylated butanetriols with paraformaldehyde.

Several racemic compounds of 1,3-dioxepane series have been separated into enantiomers using enzymatic acylation by lipase PS. For the optically active alcohols, our experimental data suggest that the developed approach leads to enantiomerically pure compounds with the enantiomeric excess close to 100%.

Biological screening experiments have demonstrated that several compounds possess promising antifungal activity. Thus, the leading compound **32** with S-configuration of both stereocenters has expressed antifungal activity against four highly aggressive clinical isolates of fungi belonging to *C. albicans*, *A. fumigatus*, *E. floccosum*, and *M. pusillus* species, which is comparable with that of terbinafine and higher than activity of fluconazole. Of note, the synthesized 1,3-dioxanes were inactive against the studied fungal strains. The obtained chemotype represents a promising starting point for the development of viable antifungal drug candidates.

Data Availability

All the necessary analytical and other data are presented in the manuscript.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

Acknowledgments

This paper is dedicated to Professor Evgenii Naumovich Klimovitskii, the scientist, who made a significant contribution to this direction of research, and the teacher, whose memory will remain forever in our hearts. This work was supported by Programs of Competitive Growth of Kazan (Volga region) Federal University and I.M. Sechenov First Moscow State Medical University.

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