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Synthesis and antimicrobial activities of unsymmetrical thioditetrazoles and their precursor thiotetrazoles

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Abstract: In this study, a synthetic route to access unsymmetrical ditetrazoles was developed. By using this method, the first examples of unsymmetrical thioditetrazole compounds were synthesized. In vitro, antibacterial efficacy studies were carried out for all the thioditetrazoles and their precursor thiotetrazoles against ten bacteria. The synthesized compounds showed a strong antibacterial effect against pathogenic Gram-negative bacteria, especially Escherichia coli, Salmonella typhi and Pseudomonas aeruginosa (up to 23 mm).

Keywords: Tetrazole; thiotetrazole; dithiotetrazole; antibacterial activity; antifungal activity.

1. Introduction

Tetrazole is a five-membered, synthetic, nitrogen-rich heterocyclic compound[1]. Although it is widely used in the explosive industry[2], it is quite stable compared to pentazole, which shows explosive properties even at low temperatures[3]. The tetrazolate anion formed by deprotonation of tetrazole is stabilized by the electron withdrawal of the four sp^2 hybridized nitrogens in the structure. This resonance stability allows tetrazole to have pKa values like carboxylic acids[3-5]. Thanks to this property, tetrazoles have been used in pharmaceuticals as lipophilic pharmacophore and carboxylic acid bioisosteres[6] and have played a major role in the development of biologically active molecules. As a result, the tetrazole ring is a fragment of many modern antibacterials[7,8], antihypertensives[9], antiallergics[10], and anti-inflammatory[11] agents. The biological and chemical properties of tetrazoles can be changed by different substituents attached to tetrazoles. While 5-substituted tetrazoles are carboxylic acid isosteres[12], 1,5-disubstituted tetrazoles are cis-amide bond isosteres found in peptic

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bonds[13]. Compared with cis-amide bonds, it has been reported that the metabolic stability of the 1,5-disubstituted tetrazoles is higher[14].

In recent years, diseases such as Gram (-) meningitis, Pseudomonas pneumonia, penicillinase-producing Neisseria gonorrhoeae, streptococcal endocarditis, melioidosis, Gram-negative sepsis and Gram (-) osteomyelitis caused by drug-resistant Gram (-) bacteria have increased considerably[15]. Considering this antibiotic resistance, the synthesis and development of new-generation cephalosporin-like antibiotics have become very important.

Due to their strong antioxidant properties, sulfur has begun to be incorporated into tetrazole structures[16,17]. In 2015, Morjan et al.[18] synthesized only symmetrical thioditetrazole that was shown to not mimic the antibiotics against Gram-positive and Gram-negative bacteria together. In 2021, our group synthesized two novel N-substituted thiotetrazole derivatives[19]. Both derivatives have shown a wide range of antimicrobial activity for the Gram (-) and Gram (+) bacteria together.

In recent years, interest in compounds bearing two tetrazole units has increased. In 2018 Deng et. al. studied on some symmetrical ditetrazole derivatives' inhibition effect on cold-rolled steel[20]. In 2018 Szimhardt et al. studied some symmetrical energetic ditetrazoles coordination properties with some cations[21]. In 2014 Xiao-Hong and Rui-Zhou focused on the energetical properties of some symmetrical ditetrazoles containing electron-donor and electron-withdrawing groups[22]. However, to the best of our knowledge, no study has been made on the antibacterial properties of ditetrazoles.

2. Background

To date, the synthesis of any unsymmetrical ditetrazole has not yet been achieved. In this paper, we described a synthetic route to achieve unsymmetrical ditetrazoles. By using this route, we synthesized the first examples of unsymmetrical thioditetrazoles. We then investigated the antimicrobial properties of the obtained thioditetrazoles and their precursor thiotetrazole compounds. The motivation of the study was depicted through the structure of thioditetrazole in Figure 1.

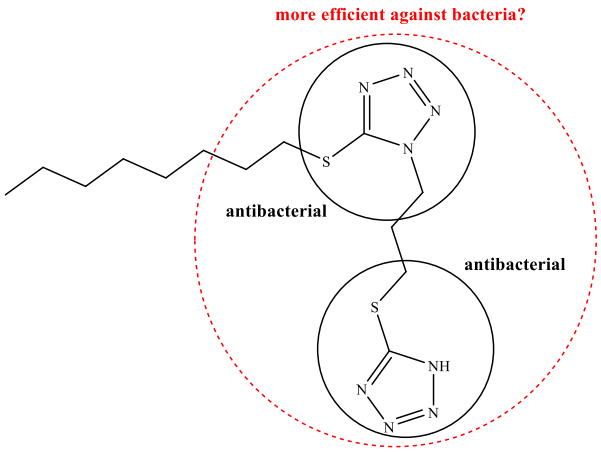


Figure 1. Motivation of the study

3. Experimental

3.1. Materials and Methods

All chemicals were used as analytical grade and directly. The completion of the reaction was performed by thin-layer chromatography (TLC) using silica gel coated with fluorescent indicator F254 and the spots were visualized by a UV-Visible lamp. ^{1}H and ^{13}C-APT NMR spectra were obtained with Bruker 300 Hz NMR instrument using $CDCl_3$ as solvents and TMS as an internal reference. High resolution mass (HR-MS) analyses were performed on Agilent TOF LC/MS 1200/6210 Mass Spectrometer (**5a** and **5b**) or Waters Quattro Premier HR-LCMS (**5c**) Mass Spectrometer using acetonitrile as a solvent. HR-MS analyses were made only for thioditetrazole compounds **5a-c.**

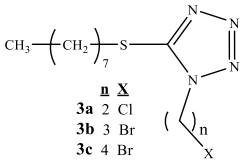
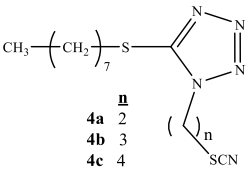
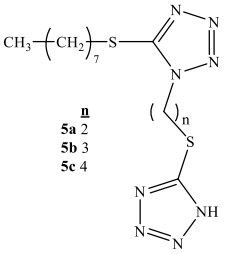
3.2. Test Microorganisms and Determination of Antimicrobial Activity

Staphylococcus aureus ATCC 25923, *Escherichia coli* ATCC 1280, *Salmonella typhi* H NCTC 901.8394, *Staphylococcus epidermidis* ATCC 12228, *Micrococcus luteus* ATCC 9341, *Bacillus cereus* RSKK 863, *Klebsiella pneumonia* ATCC 27853, *Proteus vulgaris* RSKK 96026, *Pseudomonas aeroginosa* ATCC 27853, *Enterobacter aerogenes* ATCC 51342 and *Candida albicans* Y-1200-NIH were used for determiantion of antibacterial and antifungal potential of the compounds. The 1-(2-chloroethyl)-5-(octylthio)-1*H*-tetrazole (**3a**), 1-(3-bromopropyl)-5-(octylthio)-1*H*-tetrazole (**3b**), 1-(4-bromobutyl)-5-(octylthio)-1*H*-tetrazole (**3c**), 1-(2-thiocyanatoethyl)-5-(octylthio)-1*H*-tetrazole (**4a**), 1-(3-thiocyanatopropyl)-5-(octylthio)-1*H*-tetrazole (**4b**), 1-(4-thiocyanatobutyl)-5-(octylthio)-1*H*-tetrazole (**4c**), 1-(2-((1*H*-tetrazole-5-yl)thio)ethyl)-5-(octylthio)-1*H*-tetrazole (**5a**), 1-(3-((1*H*-tetrazole-5-yl)thio)propyl)-5-(octylthio)-1*H*-tetrazole (**5b**), 1-(4-((1*H*-tetrazole-5-yl)thio)butyl)-5-(octylthio)-1*H*-tetrazole (**5c**) were screened for their antimicrobial activity by the well-diffusion method[23,24]. against six Gram-negative bacteria (*S. typhi*, *E. coli*, *E. aerogenes*, *K. pneumonia*, *P. vulgaris*, *P. aeroginosa*), four Gram-positive bacteria (*S. aureus*, *S. epidermis*, *M. luteus*, *B. cereus*) and one yeast (*C. albicans*) The compounds were kept dry at room temperature and dissolved 103 μM in DMSO. DMSO was used as solvent for compound and also for control. DMSO was found to have not antimicrobial activity against any of the pathogenic microorganisms.1% (v/v) of the 24h broth culture (pathogenic bacteria and yeast) containing 106 CFU/mL was placed in sterile plate. The mean value for the three wells was used to calculate the zone of growth inhibition of each pathogenic bacteria and yeast (to compare the degree of inhibition, bacteria and yeast were tested for resistance to 4 standard antibiotics (Kanamycin, Sulfamethoxazole, Ampicillin, Amoxicillin) and one anticandidal (Nystatin))[25-27].

4. Present Study

In the present work, we synthesized unsymmetrical thioditetrazole derivatives that have long aliphatic chains including ethylene, propylene, and butylene bridges. The synthesized compounds and their precursors depicted below (Table 1). The yields of the compounds are given as the average yield of each molecule yields.

Table 1. Synthesized compounds and their yields

Compd. 3a-c	Yield (%)	Compd. 4a-c	Yield (%)	Compd. 5a-c	Yield (%)
	**3a** 74% **3b** 47% **3c** 31%		**4a** 82% **4b** 82% **4c** 59%		**5a** 48% **5b** 67% **5c** 78%

4.1. Synthesis and Spectral Data

Compounds **1**[28] and **2**[29] were synthesized according to literature procedures.

*4.1.1. Synthesis of haloalkylthiotetrazole (**3a-c**)*

Anhydrous K_2CO_3 (6,6 mmol) was dissolved in DMF (20 mL) in a beaker. 5-octyl-1*H*-thiotetrazole 2 (6,6 mmol) was added to a beaker and stirred for 1 hr at room temperature. Alkyldihalides (39,6 mmol) were put into a round bottom flask. Then K_2CO_3 solution was poured into the solution of thiotetrazole. The mixture was stirred at room temperature. After the completion of the reaction, iced water was added to the reaction mixture and the compound was extracted with ethyl acetate. The collected organic phase was dried on sodium sulfate. Ethyl acetate was removed in vacuo. The crude product was purified by column chromatography (***3a-c***).

*1-(2-Chloroethyl)-5-(octylthio)-1H-tetrazole (**3a**)*: Colorless viscous liquid. Yield: 74%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.88 (t, *J*=6.3 Hz, 2H), 4.02 (t, *J*=6.3 Hz, 2H), 3.19 (t, *J*=7.4 Hz, 2H), 1.75-1.60 (m, 2H), 1.52-1.15 (m, 10H), 0.87 (t, *J*=6.6 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.9, 54.2, 40.7, 32.1, 31.7, 29.4, 29.1, 28.9, 28.6, 22.6, 14.0. Anal. calcd. for $C_{11}H_{21}ClN_4NaS$: HRMS: *m/z* 299.1082 [*M*+Na]$^+$ (calcd. 299.1073).

*1-(3-Bromopropyl)-5-(octylthio)-1H-tetrazole (**3b**)*: Colorless viscous liquid. Yield: 47%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.76 (t, *J*=6.6 Hz, 2H), 3.44 (t, *J*=6.3, 2H), 3.15 (t, *J*=7.32, 2H), 2.55 (m, 2H), 1.75-.650 (m, 2H), 1.53-1.18 (m, 10H), 0.88 (t, *J*=6.7 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.7, 51.3, 32.1, 31.8, 31.7, 29.5, 29.1, 29.0, 28.8, 28.6, 22.6, 14.0. Anal. calcd. for $C_{12}H_{23}BrN_4NaS$: HRMS: *m/z* 357.0727 [*M*+Na]$^+$ (calcd. 357.0724).

*1-(4-Bromobutyl)-5-(octylthio)-1H-tetrazole (**3c**)*: Colorless viscous liquid. Yield: 31%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.61 (t, *J*=6.8 Hz, 2H), 3.43 (t, *J*=6.4 Hz, 2H), 3.26 (t, *J*=7.35 Hz, 2H), 2.19-2.00 (m, 2H), 1.89-1.70 (m, 2H), 1.74-1.55 (m, 2H), 1.54-1.13 (m, 10H), 0.88 (t, *J*=6.6 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 163.7, 51.4, 31.3, 31.3, 30.9, 28.7, 28.2, 28.2, 28.2, 27.8, 21.7, 13.2. Anal. calcd. for $C_{13}H_{25}BrN_4NaS$: HRMS: *m/z* 371.0879 [*M*+Na]$^+$ (calcd. 371.0881).

*4.1.2 Synthesis of thiocyanato alkylthiotetrazoles (**4a-c**)*

Potassium thiocyanate (0.5 mmol) and ***3a-c*** (0.5 mmol) were dissolved in ethyl alcohol (20 mL) and refluxed until the reaction was completed (TLC). Ethyl alcohol was removed in vacuo. The residue was purified by column chromatography (***4a-c***).

1-(2-Thiocyanatoethyl)-5-(octylthio)-1H-tetrazole (***4a***): Beige liquid. Yield: 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.99 (t, *J*=6.3 Hz, 2H), 3.55 (t, *J*= 6.5 Hz, 2H), 3.21 (t, *J*= 7.32 Hz, 2H), 1.76-1.60 (m, 2H), 1.51-1.17 (m, 10H), 0.89 (t, *J*= 4.8 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.9, 109.3, 50.9, 31.3, 30.9, 28.6, 28.3, 28.2, 27.8, 21.8, 13.3. Anal. calcd. for $C_{12}H_{21}N_5NaS_2$: HRMS: *m/z* 322.1134 [*M*+Na]$^+$ (calcd. 322.1136).

1-(3-Thiocyanatopropyl)-5-(octylthio)-1H-tetrazole (***4b***): Beige liquid. Yield: 82%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.90 (t, *J*= 6.3 Hz, 2H), 3.16 (t, *J*= 7.35 Hz, 2H), 3.02 (t, *J*= 6.5 Hz, 2H), 2.45-2.20 (m, 2H), 1.95-1.60 (m, 2H), 1.53-1.18 (m, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 165.1, 112.2, 50.5, 32.1, 31.7, 30.5, 29.5, 29.1, 29.1, 29.0, 28.6, 22.6, 14.1. Anal. calcd. for $C_{13}H_{24}N_5S_2$: HRMS: *m/z* 314.1469 [*M*+H]$^+$ (calcd. 314.1473)

1-(4-Thiocyanatobutyl)-5-(octylthio)-1H-tetrazole (***4c***): Beige liquid. Yield: 59%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.64 (t, *J*= 6.8 Hz, 2H), 3.28 (t, *J*= 7.35 Hz, 2H), 3.00 (t, *J*= 7.0 Hz, 2H), 2.20-2.10 (m, 2H), 1.91-1.70 (m, 2H), 1.76-1.60 (m, 2H), 1.54-1.14 (m, 10H), 0.89 (t, *J*= 6.5 Hz, 2H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.7, 111.6, 52.2, 33.1, 32.1, 31.8, 29.5, 29.1, 29.0, 28.6, 27.3, 26.7, 22.6, 14.1. Anal. calcd. for $C_{14}H_{25}N_5NaS_2$: HRMS: *m/z* 350.1465 [*M*+Na]$^+$ (calcd. 350.1449).

*4.1.3. Synthesis of thioditetrazole (**5a-c**)*

$Et_3N.HCl$ (0,655 mmol) and sodium azide (0.655 mmol) was dissolved in toluene (10 mL) at room temperature After the mixture color had turned to salmon-pink, related alkyl thiotetrazoles were added to the mixture and refluxed. After the reaction was completed the reaction solvent was evaporated. Water (10 mL) was added to the mixture and 3M HCl (aq) was added until the pH was 2-3. The formed solid was filtered and dried (***5a-c***).

1-(2-((1*H*-tetrazole-5-yl)thio)ethyl)-5-(octylthio)-1*H*-tetrazole (***5a***): White crystals. M.p. 82 ºC. Yield: 48%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.05 (t, *J*= 6.2 Hz, 2H), 3.88 (t, *J*=6.2 Hz, 2H), 3.18 (t, *J*= 7.3 Hz, 2H), 1.73-1.60 (m, 2H), 1.47-1.13 (m, 10H), 0.87 (t, *J*= 6.2 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.7, 165.9, 56.8, 36.9, 36.5, 36.0, 34.4, 34.1, 33.8, 33.4, 27.4, 18.8. Anal. calcd. for $C_{12}H_{21}N_8S_2$: HRMS : *m/z* 341.1388 [*M*-H]$^+$ (calcd. 341.1331).

1-(3-((1*H*-tetrazole-5-yl)thio)propyl)-5-(octylthio)-1*H*-tetrazole (***5b***): White crystals. M.p. 45 ºC. Yield: 67%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.73 (t, *J*= 6.5 Hz, 2H), 3.42 (t, *J*= 6.9 Hz, 2H), 3.13 (t, *J*= 7.0 Hz, 2H), 2.54-2.40 (m, 2H), 1.74-1.50 (m, 2H), 1.48-1.21 (m, 10H), 0.87 (t, *J*= 6.4 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.9, 154.5, 51.5, 32.2, 31.7, 29.5, 29.4, 29.1, 29.0, 28.7, 28.6, 22.6, 14.1. Anal. calcd. for $C_{13}H_{25}N_8S_2$: HRMS: *m/z* 357.1614 [*M*+H]$^+$ (calcd. 357.1644).

1-(4-((1*H*-tetrazole-5-yl)thio)butyl)-5-(octylthio)-1*H*-tetrazole (***5c***): White crystals. M.p. 48 ºC. Yield: 78%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.63 (t, *J*= 6.8 Hz, 2H), 3.35 (t, *J*= 7.2 Hz, 2H), 3.15 (t, *J*= 7.1 Hz, 2H), 2.19-2.10 (m, 2H), 1.88-1.60 (m, 2H), 1.73-1.50 (m, 2H), 1.50-1.14 (m, 10H), 0.88 (t, *J*= 6.5 Hz, 3H). ^{13}C NMR (300 MHz, $CDCl_3$): δ 164.7, 155.3, 52.7, 32.3, 31.8, 31.7, 29.4, 29.1, 29.0, 28.6, 27.8, 26.3, 22.6, 14.1. Anal. calcd. for $C_{14}H_{27}N_8S_2$: HRMS: *m/z* 371.1818 [*M*+H]$^+$ (calcd. 371.1800).

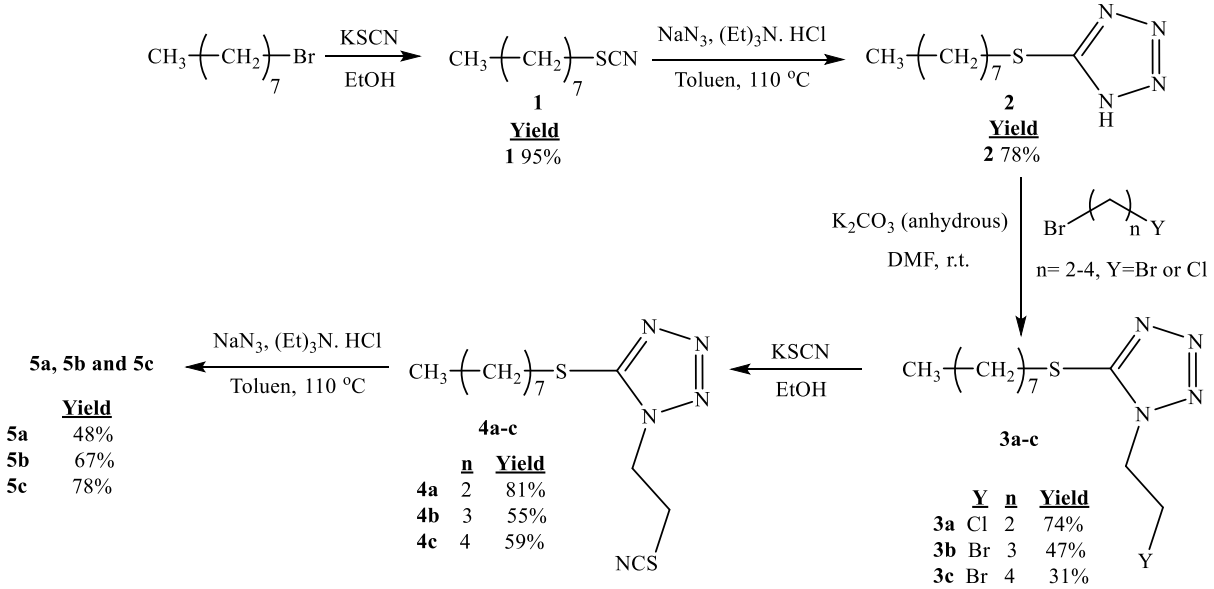


Figure 2. Synthetic pathway of the compounds **3-5**

As an example, the spectroscopic characterization of compound **5a** was discussed. In the ^{1}H NMR spectrum the protons on long alkyl chain were observed between 0.87-3.18 ppm. The splitting patterns of these protons are as expected. The protons between two tetrazole units were observed as triplets at 4.73 and 3.42 ppm. The twelve carbons on the compounds were observed at expected shifting values at the ^{13}C NMR spectrum. The found mass of the compound by HRMS (341.1388) is in accordance with the calculated value (341.1331). The spectra of all other compounds also matched their structure.

4.2. Antimicrobial Activity

The synthesized compounds showed variable activity (11 mm-23 mm) on the growth of the pathogenic bacteria yeast used, and the inhibition rates mainly differed between medium and high activities. In addition, compounds were more effective in Gr (-) bacteria than Gr (+) bacteria (Figure 4). The related data were summarized in supporting information (Table S1).

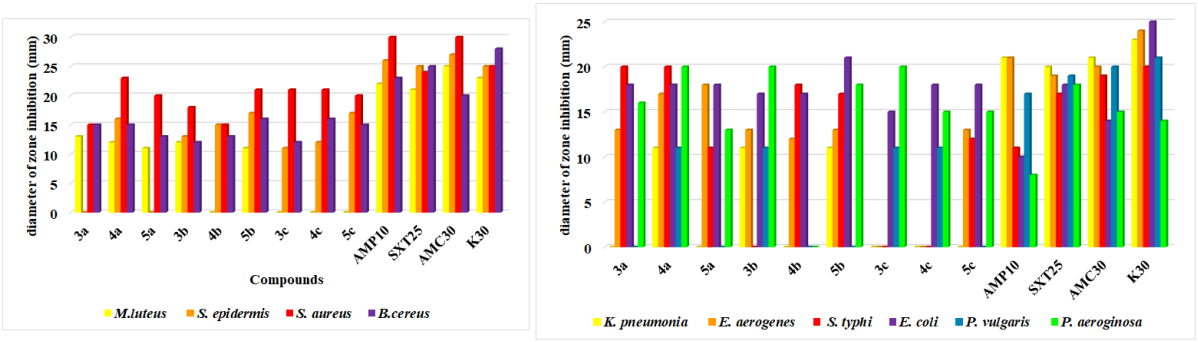


Figure 3. Biological activity of the synthesized compounds against Gram-positive and Gram-negative bacteria respectively

Compound **3a** showed higher inhibitory activity in *P. aeroginosa* (16 mm) than AMP10 (8 mm), AMC30 (15 mm) and K30 (14 mm). Bacteria of the genus Pseudomonas are widespread in nature and cause opportunistic infections and nosocomial infections. Among them, *P. aeruginosa* ranks first among nosocomial infections and can develop resistance to various antibiotics and cause high mortality and morbidity due to infection[30-32]. In addition, this compound showed the same inhibitory effect as K30 (20 mm) on *Salmonella typhi*, but showed higher activity than SXT25, AMC30, AMP10 (respectively; 17 mm, 19 mm, 11 mm). Compound **3c** showed a greater inhibitor effect in Gr (-) *P. aeroginosa* (20 mm) than all of standard antibiotics. In addition, this compound showed higher inhibitory activity than AMP10 (10 mm) and AMC30 (14 mm). Compound 4c demonstrated higher inhibitory activity in *P.aeroginosa* (15 mm) and E.coli (18 mm). The other antimicrobial bioassay study results are discussed in supporting information.

From the interpretation of the data given in Table S1, it was seen that compounds prepared in this work recorded high antimicrobial activity similar to the reference drugs used and could help antimicrobial agents. As a result, it was concluded that these compounds are more effective in Gr (-) bacteria than Gr (+) bacteria. The potential cause for this may be the presence of the outer impermeable membrane, thin peptidoglycan monolayer, periplasmic space, and cell wall composition in Gram-negative bacteria[33].

In conclusion, we developed a five-step route to access unsymmetrical thioditetrazoles. Using this method, we synthesized unsymmetrical thioditetrazoles and their precursors and studied their antimicrobial properties. These compounds showed high antimicrobial effects against *E. coli*, *S. typhi*, and *P. aeruginosa*. To our surprise, the precursor halogen and thiocyanate-bearing compounds also showed a high antibacterial effect on these pathogen Gram-negative bacteria. The inhibition zones of all these compounds were comparable and, in some cases, superior to the commercial antibiotics. Interestingly, the length of the alkyl chains was also observed to change the inhibition zones of the compounds. The obtained data showed that all these compounds can be used as antimicrobial agents against pathogenic microorganisms or as an additive to antimicrobial products.

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Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/organic-communications

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