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Synthesis and biological studies of novel hydroxyacetophenone-tetrazole hybrids

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Abstract: A series of novel hybrid compounds was synthesized where 2′-hydroxyacetophenone and *N*-alkylated thiotetrazole were coupled via methylene spacers of different lengths. The structures of the compounds were characterized by spectroscopic techniques, including the ^{1}H- and ^{13}C-NMR, FT-IR, and HRMS methods. The antimicrobial activities of the title compounds were evaluated against clinical isolates of Gram-positive and negative bacterial and fungal species. All compounds showed a broad spectrum of antimicrobial activity and inhibited all bacteria and fungi that tested with MIC values ranging from 4 to 128 µg/ml. **4a** and **5d** were the most active antibacterial members.

Keywords: Hydroxyacetophenone; tetrazole; hybrid; antimicrobial activity.

1. Introduction

Small molecules are used as research tools to study biological functions. Hydroxyacetophenones are small molecules with various biological activities (Figure 1). 2′-Hydroxy-4′-methoxyacetophenone (**a**) is used as an antipyretic, analgesic, and anti-inflammatory agent.[1,2] 3′-Hydroxy-4′-methoxyacetophenone (**b**) has analgesic activity and suppresses gastrointestinal motility.[3] 2′-Hydroxy-6′-methoxyacetophenone (**c**) has antimutagenic activity against *Salmonella Typhimurium*.[4] Morita *et al.* reported six hydroxyacetophenone derivatives that inhibited the early antigen activation of the Epstein-Barr virus.[5] 2′,4′-Dihydroxy-3′-methylacetophenone (**d**) has potent anti-inflammatory and antiasthmatic activity.[6] Xanthoxylin (**e**), a hydroxyacetophenone isolated from *Melicope borbonica*, has an antifungal activity against *Penicillium expansum* and *Candida albicans*.[7] LY171883 (**f**), a 2′-hydroxyacetophenone, is a selective cysteinyl-leukotriene receptor type 1 ($CysLT_1$) antagonist.[8]

Hydroxyacetophenones have the potential to exhibit a remarkable activity against bacterial and fungal pathogens. For example, 2′-hydroxy-3′,4′,6′-trimethoxyacetophenone is one of the antibacterial agents with significant activities against *Pseudomonas aeruginosa* and *Staphylococcus aureus*.[9] 2′,6′-Dihydroxy-4′-geranyloxyacetophenone exhibits a strong antimicrobial activity against major oral pathogens.[10] Dihydroxyacetophenone isomers in coffee residue (2′,6′-, 2′,4′-, 3′,4′-, 2′,5′-, and 3′,5′-dihydroxyacetophenone) were found to have antimicrobial activity against tested bacteria.[11] 4'-Hydroxyacetophenone[12], 2′,4′-dihydroxy-5′-methylacetophenone[13] and 2′-hydroxy-4′,6′-dimethoxy-

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acetophenone[7] are hydroxyacetophenones that exhibit antifungal activities against the fungi *Cladosporium cucumerinum*, *Glomerella cingulata* and *Penicillium expansum*, respectively.

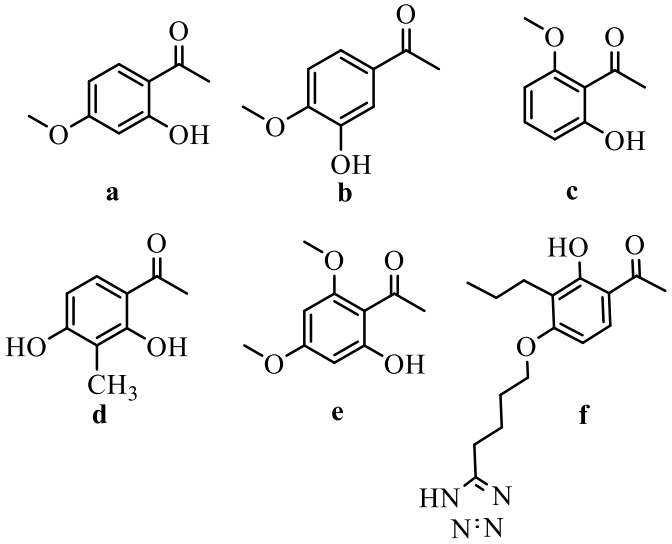


Figure 1. Some hydroxyacetophenones with various biological activities

Tetrazole is a heterocyclic small azaarene with 6π-electrons, consisting of four nitrogen atoms and one carbon atom. It plays an important role in medicinal chemistry. Tetrazole is used as the bioisostere of carboxylic acid in drug design since the substitution of tetrazole for carboxylic acid improves the physicochemical properties of a molecule.[14,15] It also increases the efficacy, lipophilicity, metabolic stability and half-life of the drug while reducing its toxicity.[16,17] Moreover, tetrazole-containing compounds have the potential to be used as antibacterial, antifungal, antitumor, antihypertensive, anti-asthmatic, antihyperlipidemic, and anti-inflammatory agents.[18]

N-Substituted thiotetrazoles are the structural components of some antibacterial agents used to treat or prevent certain bacterial infections.[17-19] For example, several cephalosporin antibiotics (cefmenoxime, cefamandole, cefpiramide, ceforanide, and cefonicid) contain a *N*-methylthiotetrazole moiety in their structure.[19-21] 2-(1-Allyl-1*H*-tetrazol-5ylsulfanyl)-*N*-arylacetamides,[22] 3-phenyl-5-[(1-phenyl-1*H*-tetrazol-5-yl)thio]-4*H*-1,2,4-triazol-4-amine,[23] and 1-benzyl-5-[(3-bromopropyl)thio]-1*H*-tetrazole[24] also contain *N*-substituted thiotetrazole in their structure, and possess antibacterial activities.

One of the strategies for designing a novel drug is to combine two pharmacophores. The resulting hybrid type molecule may have several advantages over its constituents, such as an improved pharmacokinetic profile, a synergistic effect on the pharmacological potential, and a reduction in the risk of drug resistance.[25,26] In our previous study, we synthesized 2′-hydroxyacetophenones coupled to 1-propyl-1*H*- and 2-propyl-2*H*-thiotetrazole via a trimethylene linker and evaluated their antimicrobial activities.[27] Now, we report the synthesis and antimicrobial activities of 2'-hydroxyacetophenones coupled to *N*-alkylated thiotetrazoles via methylene spacers of various lengths (Figure 2).

2. Experimental

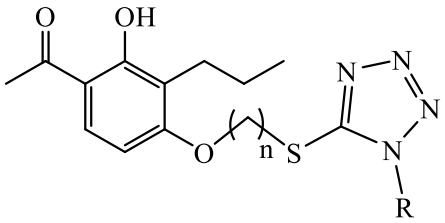
2.1. Chemicals and Instruments

All chemicals that were used in this study were obtained from Merck, Aldrich, or Acros Organics. FTIR spectra were recorded on a Thermo Nicolet 6700 ATR spectrometer. ^{1}H NMR and ^{13}C APT spectra were recorded using a Bruker Avance DPX-300 NMR spectrometer. The compounds were isolated and purified by using Merck Silica Gel 60 (0.063-0.2 mm). Mass spectra were recorded using Waters LCT Premier XE LTOF instrument. Melting points were recorded using a Stuart SMP-30

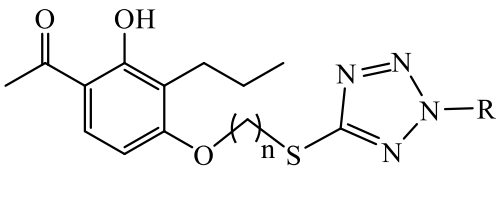
melting point instrument and were not corrected. Analytical data are reported in the Supporting Information section.

2.2. Chemistry

Compounds **4a-4f** and **5d-5f** were synthesized according to a previously published protocol.[27] Compounds **5a, 5b**, and **5c** could not be isolated. The structures of **4a-4f** and **5d-5f** were identified for the first time.



4a-4f



5d-5f

a; R= **-**$CH_2CH_2CH_3$, n=2

b; R= **-**$CH_2CH_2CH_2CH_3$, n=2

c; R= **-**$CH_2C_6H_5$, n=2

d; R= -$CH_2CH_2CH_2CH_3$, n=3

e; R= **-**$CH_2C_6H_5$, n=3

f; R= -$CH_2CH_2CH_3$, n=4

Figure 2. The hydroxyacetophenones coupled to *N*-alkylated thiotetrazoles via methylene spacers

*2.2.1. Synthesis of 1-[4-(3-((1H-tetrazol-5-yl)thio)alkoxy)-2-hydroxy-3-propylphenyl]ethanone (**3**)*:

1-[4-(3-((1H-tetrazol-5-yl)thio)alkoxy)-2-hydroxy-3-propylphenyl]ethanone (**3**) was synthesized by the method known in the literature. [27-29]

1-[4-(3-((1H-tetrazol-5-yl)thio)ethoxy)-2-hydroxy-3-propylphenyl]ethanone: White solid, 98%, mp: 120-122 °C, lit. 121-122 °C.[28,29] FTIR υ_{max} (cm^{-1}):3600-3500 (-OH), 3300-3100 (N-H), 3079 (Ar-H), 2924 (-C-H), 1622 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.74 (s, 1H, OH), 7.60 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ar-H), 6.48 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ar-H), 4.45 (t, 2H, $^3J_{HH}$ = 6.0 Hz, CH_2), 3.75 (t, 2H, $^3J_{HH}$ = 6.0 Hz, CH_2), 2.63 (t, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2), 2.57 (s, 3H, CH_3), 1.60-1.40 (m, 2H, CH_2), 0.94 (t, 3H, $^3J_{HH}$ = 7.4 Hz, CH_3).

1-[4-(3-((1H-tetrazol-5-yl)thio)propoxy)-2-hydroxy-3-propylphenyl]ethanone: White solid, 95%, mp: 130-132 °C, lit. 131-133 °C. [28,29] FTIR υ_{max} (cm^{-1}):3600-3500 (-OH), 3300-3100 (N-H), 3091 (Ar-H), 2924 (-C-H), 1626 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.73 (s, 1H, OH), 7.58 (d, 1H, $^3J_{HH}$ = 8.9 Hz, Ar-H), 6.43 (d, 1H, $^3J_{HH}$ = 8.9 Hz, Ar-H), 4.18 (t, 2H, $^3J_{HH}$ = 5.7 Hz, CH_2), 3.50 (t, 2H, $^3J_{HH}$ = 5.7 Hz, CH_2), 2.64 (t, 2H, $^3J_{HH}$ = 7.3 Hz, CH_2), 2.56 (s, 3H, CH_3), 2.20-2.40 (m, 2H, CH_2), 1.40-1.60 (m, 2H, CH_2), 0.90 (t, 3H, $^3J_{HH}$ = 7.3 Hz, CH_3).

1-[4-(3-((1H-tetrazol-5-yl)thio)butoxy)-2-hydroxy-3-propylphenyl]ethanone: White solid, 95%, mp: 84-85 °C, lit. 84-84 °C. [28,29] FTIR υ_{max} (cm^{-1}):3400-3300 (-OH), 3300-3100 (N-H), 3052 (Ar-H), 2948 (-C-H), 1631 (C=O). ^{1}H-NMR ($CDCl_3$) δ (ppm): 12.71 (s, 1H, OH), 7.58 (d, 1H, $^3J_{HH}$ = 8.9 Hz, Ar-H),

6.41 (d, 1H, $^{3}J_{HH}$ = 9.0 Hz, Ar-H), 4.07 (t, 2H, $^{3}J_{HH}$ = 5.5 Hz, CH_2), 3.43 (t, 2H, $^{3}J_{HH}$ = 6.7 Hz, CH_2), 2.60 (t, 2H, $^{3}J_{HH}$ = 7.4 Hz, CH_2), 2.58 (s, 3H, CH_3), 1.90-2.10 (m, 4H, $2CH_2$), 1.40-1.60 (m, 2H, CH_2), 0.90 (t, 3H, $^{3}J_{HH}$ = 7.4 Hz, CH_3).

*2.2.2. General procedure for synthesis of hydroxyacetophenone-tetrazole hybrids **4a-4f** and **5d-5f:*** [27]

The appropriate 1-[4-(3-((1H-tetrazol-5-yl)thio)alkoxy)-2-hydroxy-3-propylphenyl]ethanone **3** (0.008 mol) was dissolved in 25 mL of DMF. K_2CO_3 (2.21 g, 0.016 mol) was added and stirred for 1 hour at room temperature. The alkyl halide (0.016 mol) was added dropwise and heated under a condenser at 80ºC for 21-23 h. The solution was allowed to cool to room temperature, poured into ice water and extracted with ethyl acetate (4x25 mL). The organic layers were combined, dried over Na_2SO_4, and filtered. The filtrate was concentrated under vacuum and the compounds were separated from each other by column chromatography on silica gel (1:5 ethyl acetate-petroleum ether) to obtain the targed compounds. Compounds **5a, 5b** and **5c** could not be isolated. The structures of **4a-4f** and **5d-5f** were identified for the first time.

*1-(2-hydroxy-3-propyl-4-(2-((1-propyl-1H-tetrazol-5-yl)thio)ethoxy)phenyl)ethan-1-one (**4a**)*: Viscous liquid, 77%. FTIR υ_{max} (cm^{-1}): 3082 (Ar-H), 2980 (-C-H), 1643 (-C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 12.73 (s, 1H, OH), 7.57 (d, 1H, $^{3}J_{HH}$ = 9.0 Hz, Ar-H), 6.47 (d, 1H, $^{3}J_{HH}$ = 9.0 Hz, Ar-H), 4.53 (t, 2H, $^{3}J_{HH}$ = 7.1 Hz, CH_2), 4.38 (t, 2H, $^{3}J_{HH}$ = 6.5 Hz, CH_2), 3.60 (t, 2H, $^{3}J_{HH}$ = 6.5 Hz, CH_2), 2.62 (t, 2H, $^{3}J_{HH}$ = 7.4 Hz, CH_2), 2.55 (s, 3H, CH_3), 2.03 (sext, 2H, $^{3}J_{HH}$ = 7.1 Hz, CH_2), 1.53 (sext, 2H, $^{3}J_{HH}$ = 7.4 Hz, CH_2), 0.90-1.00 (m, 6H, $2CH_3$). ^{13}C-APT (75 MHz, $CDCl_3$) δ (ppm): 202.9 (C=O), 163.3 (C Ar), 162.2 (C Ar), 162.1 (C Ar), 130.1 (C Ar), 118.5 (C Ar), 114.4 (C Ar), 102.7 (C Ar), 69.7 (CH_2), 55.0 (CH_2), 32.7 (CH_2), 26.4 (CH_2), 26.3 (CH_3), 24.6 (CH_2), 22.9 (CH_2), 13.7 (CH_3), 11.2 (CH_3). HRMS (ESI TOF-MS) *m/z* calculated for $C_{17}H_{25}N_4O_3S$ $[M+H]^+$: 365.1647, found: 365.1631.

*1-(4-(2-((1-butyl-1H-tetrazol-5-yl)thio)ethoxy)-2-hydroxy-3-propylphenyl)ethan-1-one (**4b**)*: Viscous liquid, 74%. FTIR υ_{max} (cm^{-1}): 3072 (Ar-H), 2931 (-C-H), 1634 (-C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 12.74 (s, 1H, OH), 7.58 (d, 1H, $^{3}J_{HH}$ = 9.0 Hz, Ar-H), 6.48 (d, 1H, $^{3}J_{HH}$ = 9.0 Hz, Ar-H), 4.58 (t, 2H, $^{3}J_{HH}$ = 7.2 Hz, CH_2), 4.39 (t, 2H, $^{3}J_{HH}$ = 6.5 Hz, CH_2), 3.61 (t, 2H, $^{3}J_{HH}$ = 6.5 Hz, CH_2), 2.63 (t, 2H, $^{3}J_{HH}$ = 7.5 Hz, CH_2), 2.56 (s, 3H, CH_3), 1.99 (qu, 2H, $^{3}J_{HH}$ = 7.2 Hz, CH_2), 1.54 (sext, 2H, $^{3}J_{HH}$ = 7.5 Hz, CH_2), 1.38 (sext, 2H, $^{3}J_{HH}$ = 7.2 Hz, CH_2), 0.90-1.00 (m, 6H, $2CH_3$). ^{13}C-APT (75 MHz, $CDCl_3$) δ (ppm): 202.9 (C=O), 163.3 (C Ar), 162.5 (C Ar), 162.1 (C Ar), 130.0 (C Ar), 118.6 (C Ar), 114.4 (C Ar), 102.7 (C Ar), 66.7 (CH_2), 53.1 (CH_2), 30.8 (CH_2), 29.6 (CH_2), 26.2 (CH_3), 24.3 (CH_2), 21.9 (CH_2), 19.5 (CH_2), 14.1 (CH_3), 13.3 (CH_3). HRMS (ESI TOF-MS) *m/z* calculated for $C_{18}H_{27}N_4O_3S$ $[M+H]^+$: 379.1804; Found: 379.1782.

*1-(4-(2-((1-benzyl-1H-tetrazol-5-yl)thio)ethoxy)-2-hydroxy-3-propylphenyl)ethan-1-one (**4c**)*: Viscous liquid, 62%. FTIR υ_{max} (cm^{-1}): 3032 (Ar-H), 2958 (-C-H), 1625 (-C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 12.75 (s, 1H, OH), 7.56 (d, 1H, $^{3}J_{HH}$ = 8.9 Hz, Ar-H), 7.38 (s, 5H, Ar-H), 6.45 (d, 1H, $^{3}J_{HH}$ = 8.9 Hz, Ar-H), 5.75 (s, 2H, CH_2), 4.38 (t, 2H, $^{3}J_{HH}$ = 6.4 Hz, CH_2), 3.60 (t, 2H, $^{3}J_{HH}$ = 6.4 Hz, CH_2), 2.63 (t, 2H, $^{3}J_{HH}$ = 7.3 Hz, CH_2), 2.56 (s, 3H, CH_3), 1.54 (sext, 2H, $^{3}J_{HH}$ = 7.3 Hz, CH_2), 0.94 (t, 3H, $^{3}J_{HH}$ =7.3 Hz, CH_3). ^{13}C-APT (75 MHz, $CDCl_3$) δ (ppm): 162.1 (C Ar), 129.9 (C Ar), 129.1 (2C Ar), 129.0 (C Ar), 128.5 (2C Ar), 128.1 (C Ar), 102.7 (C Ar), 66.7 (CH_2), 57.1 (CH_2), 30.8 (CH_2), 26.3 (CH_3), 24.3 (CH_2), 21.9 (CH_2), 14.2 (CH_3). HRMS (ESI TOF-MS) *m/z* calculated for $C_{21}H_{25}N_4O_3S$ $[M+H]^+$: 413.1647; Found: 413.1661.

*1-(4-(3-((1-butyl-1H-tetrazol-5-yl)thio)propoxy)-2-hydroxy-3-propylphenyl)ethan-1-one (**4d**)*: Viscous liquid, 55%. FTIR υ_{max} (cm^{-1}): 3022 (Ar-H), 2911 (-C-H), 1624 (-C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 12.75 (s, 1H, OH), 7.60 (d, 1H, $^{3}J_{HH}$ = 9.0 Hz, Ar-H), 6.43 (d, 1H, $^{3}J_{HH}$ = 9.0 Hz, Ar-H), 4.54 (t, 2H, $^{3}J_{HH}$ = 7.1 Hz, CH_2), 4.18 (t, 2H, $^{3}J_{HH}$ = 7.0 Hz, CH_2), 3.40 (t, 2H, $^{3}J_{HH}$ = 7.0 Hz, CH_2), 2.63 (t, 2H, $^{3}J_{HH}$ = 7.5 Hz, CH_2), 2.55 (s, 3H, CH_3), 2.20-2.40 (m, 2H, CH_2), 1.96 (qu, 2H, $^{3}J_{HH}$ = 7.1 Hz, CH_2), 1.54 (sext, 2H, $^{3}J_{HH}$ = 7.5 Hz, CH_2), 1.36 (sext, 2H, $^{3}J_{HH}$ = 7.1 Hz, CH_2), 0.85-1.00 (m, 6H, $2CH_3$). ^{13}C-APT (75 MHz, $CDCl_3$) δ (ppm): 202.9 (C=O), 163.4 (C Ar), 162.5 (C Ar), 162.0 (C Ar), 130.1 (C Ar), 118.1

(C Ar), 114.2 (C Ar), 102.6 (C Ar), 66.0 (CH_2), 53.0 (CH_2), 31.0 (CH_2), 29.3 (CH_2), 28.8 (CH_2), 26.2 (CH_3), 24.3 (CH_2), 21.9 (CH_2), 19.5 (CH_2), 14.2 (CH_3), 13.2 (CH_3). HRMS (ESI TOF-MS) *m/z* calculated for $C_{19}H_{29}N_4O_3S$ $[M+H]^+$: 393.1960; Found: 393.1944.

1-(4-(3-((1-benzyl-1H-tetrazol-5-yl)thio)propoxy)-2-hydroxy-3-propylphenyl)ethan-1-one ***(4e)***: Viscous liquid, 52%. FTIR υ_{max} (cm^{-1}): 3015 (Ar-H), 2973 (-C-H), 1679 (-C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 12.74 (s, 1H, OH), 7.57 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ar-H), 7.36 (s, 5H, Ar-H), 6.41 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ar-H), 5.67 (s, 2H, CH_2), 4.15 (t, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 3.38 (t, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 2.63 (t, 2H, $^3J_{HH}$ = 7.4 Hz, CH_2), 2.55 (s, 3H, CH_3), 2.20-2.35 (m, 2H, CH_2), 1.52 (sext, 2H, $^3J_{HH}$ = 7.4 Hz, CH_2), 0.92 (t, 3H, $^3J_{HH}$ = 7.4 Hz, CH_3). ^{13}C-APT (75 MHz, $CDCl_3$) δ (ppm): 207.5 (C=O), 168.7 (C Ar), 167.1 (C Ar), 166.6 (C Ar), 137.6 (2C Ar), 134.7 (C Ar), 133.5 (2C Ar), 132.9 (C Ar), 122.8 (C Ar), 118.8 (C Ar), 107.3 (C Ar), 107.2 (C Ar), 70.5 (CH_2), 61.5 (CH_2), 33.3 (CH_2), 30.8 (CH_3), 30.5 (CH_2), 28.9 (CH_2), 26.5 (CH_2), 18.8 (CH_3). HRMS (ESI TOF-MS) *m/z* calculated for $C_{22}H_{27}N_4O_3S$ $[M+H]^+$: 427.1804; Found: 427.1810.

1-(2-hydroxy-3-propyl-4-(4-((1-propyl-1H-tetrazol-5-yl)thio)butoxy)phenyl)ethan-1-one ***(4f)***: Viscous liquid, 58%. FTIR υ_{max} (cm^{-1}): 3012 (Ar-H), 2963 (-C-H), 1639 (-C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): 12.72 (s, 1H, OH), 7.54 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ar-H), 6.39 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ar-H), 4.48 (t, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 4.00-4.10 (m, 2H, CH_2), 3.20-3.30 (m, 2H, CH_2), 2.58 (t, 2H, $^3J_{HH}$ = 7.4 Hz, CH_2), 2.49 (s, 3H, CH_3), 1.90-2.10 (m, 4H, $2CH_2$), 1.48 (sext, 2H, $^3J_{HH}$ = 7.4 Hz, CH_2), 1.10-1.30 (m, 2H, CH_2) CH_2), 0.80-1.00 (m, 6H, $2CH_3$). ^{13}C-APT (75 MHz, $CDCl_3$) δ (ppm): 202.9 (C=O), 163.7 (C Ar), 162.7 (C Ar), 162.0 (C Ar), 130.0 (C Ar), 118.1 (C Ar), 114.1 (C Ar), 102.5 (C Ar), 67.4 (CH_2), 54.8 (CH_2), 31.7 (CH_2), 28.0 (CH_2), 26.3 (CH_2), 26.2 (CH_3), 24.3 (CH_2), 22.7 (CH_2), 21.9 (CH_2), 14.1 (CH_3), 10.9 (CH_3). HRMS (ESI TOF-MS) *m/z* calculated for $C_{19}H_{29}N_4O_3S$ $[M+H]^+$: 393.1960; Found: 393.1953.

1-(4-(3-((2-butyl-2H-tetrazol-5-yl)thio)propoxy)-2-hydroxy-3-propylphenyl)ethan-1-one ***(5d)***: Viscous liquid, 44%. FTIR υ_{max} (cm^{-1}): 3025 (Ar-H), 2992 (-C-H), 1671 (-C=O). ^{1}H-NMR (300 MHz, $CDCl_3$) δ (ppm): δ 12.74 (s, 1H, OH), 7.60 (d, 1H, $^3J_{HH}$ = 8.9 Hz, Ar-H), 6.44 (d, 1H, $^3J_{HH}$ = 8.9 Hz, Ar-H), 4.10-4.25 (m, 4H, $2CH_2$), 3.55 (t, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 2.65 (t, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2), 2.58 (s, 3H, CH_3), 2.35-2.45 (m, 2H, CH_2), 1.86 (qu, 2H, $^3J_{HH}$ = 7.4 Hz, CH_2), 1.54 (sext, 2H, $^3J_{HH}$ = 7.5 Hz, CH_2), 1.30-1.50 (m, 2H, CH_2), 0.90-1.00 (m, 6H, $2CH_3$). ^{13}C-APT (75 MHz, $CDCl_3$) δ (ppm): 203.0 (C=O), 162.3 (C Ar), 162.0 (C Ar), 153.6 (C Ar), 130.1 (C Ar), 118.3 (C Ar), 114.2 (C Ar), 102.5 (C Ar), 65.8 (CH_2), 47.1 (CH_2), 30.8 (CH_2), 29.8 (CH_2), 28.9 (CH_2), 26.3 (CH_3), 24.3 (CH_2), 22.0 (CH_2), 19.5 (CH_2), 14.2 (CH_3), 13.5 (CH_3). HRMS (ESI TOF-MS) *m/z* calculated for $C_{19}H_{29}N_4O_3S$ $[M+H]^+$: 393.1960; Found: 393.1874.

1-(4-(3-((2-benzyl-2H-tetrazol-5-yl)thio)propoxy)-2-hydroxy-3-propylphenyl)ethan-1-one ***(5e)***: Viscous liquid, 47%.FTIR υ_{max} (cm^{-1}): 3052 (Ar-H), 2971 (-C-H), 1646 (-C=O). ^{1}H-(300 MHz, $CDCl_3$) δ (ppm):.74 (s, 1H, OH), 7.59 (d, 1H, $^3J_{HH}$ = 8.9 Hz, Ar-H), 7.36 (s, 5H, Ar-H), 6.40 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ar-H), 5.42 (s, 2H, CH_2), 4.11 (t, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 3.49 (t, 2H, $^3J_{HH}$ = 7.0 Hz, CH_2), 2.63 (t, 2H, $^3J_{HH}$ = 7.4 Hz, CH_2), 2.57 (s, 3H, CH_3), 2.25-2.40 (m, 2H, CH_2), 1.52 (sext, 2H, $^3J_{HH}$ = 7.4 Hz, CH_2), 0.93 (t, 3H, $^3J_{HH}$ = 7.4 Hz, CH_3). ^{13}C-APT (75 MHz, $CDCl_3$) δ (ppm): 202.8 (C=O), 162.2 (C Ar), 161.9 (C Ar), 153.5 (C Ar), 132.7 (C Ar), 128.8 (2C Ar), 128.4 (C Ar), 127.9 (2C Ar), 127.5 (C Ar), 118.1 (C Ar), 114.2 (C Ar), 102.5 (C Ar), 65.7 (CH_2), 50.8 (CH_2), 29.9 (CH_2), 28.7 (CH_2), 26.1 (CH_3), 24.2 (CH_2), 21.8 (CH_2), 14.1 (CH_3). HRMS (ESI TOF-MS) *m/z* calculated for $C_{22}H_{27}N_4O_3S$ $[M+H]^+$: 427.1804; Found: 427.1711.

1-(2-hydroxy-3-propyl-4-(4-((2-propyl-2H-tetrazol-5-yl)thio)butoxy)phenyl)ethan-1-one ***(5f)***: Viscous liquid, 40%. FT-IR υ_{max} (cm^{-1}): 3035 (Ar-H), 2948 (-C-H), 1634 (-C=O). ^{1}H-NMR ($CDCl_3$) (300 MHz, $CDCl_3$) δ (ppm): 12.72 (s, 1H, OH), 7.55 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ar-H), 6.39 (d, 1H, $^3J_{HH}$ = 9.0 Hz, Ar-H), 4.15 (t, 2H, $^3J_{HH}$ = 7.1 Hz, CH_2), 4.05 (t, 2H, $^3J_{HH}$ = 5.6 Hz, CH_2), 3.41 (t, 2H, $^3J_{HH}$ = 6.8 Hz, CH_2), 2.58 (t, 2H, $^3J_{HH}$ = 7.4 Hz, CH_2), 2.52 (s, 3H, CH_3), 1.75-2.10 (m, 6H, $3CH_2$), 1.30-1.60 (m, 2H, CH_2), 0.80-1.00 (m, 6H, $2CH_3$). ^{13}C-APT (75 MHz, $CDCl_3$) δ (ppm): 202.9 (C=O), 162.6 (C Ar), 162.0 (C

Ar), 153.6 (C Ar), 130.1 (C Ar), 118.1 (C Ar), 114.1 (C Ar), 102.6 (C Ar), 67.3 (CH_2), 48.8 (CH_2), 32.8 (CH_2), 28.0 (CH_2), 26.2 (CH_2), 26.2 (CH_3), 24.3 (CH_2), 22.4 (CH_2), 21.9 (CH_2), 14.2 (CH_3), 10.9 (CH_3). HRMS (ESI TOF-MS) *m/z* calculated for $C_{19}H_{29}N_4O_3S$ $[M+H]^+$: 393.1960; Found: 393.1957.

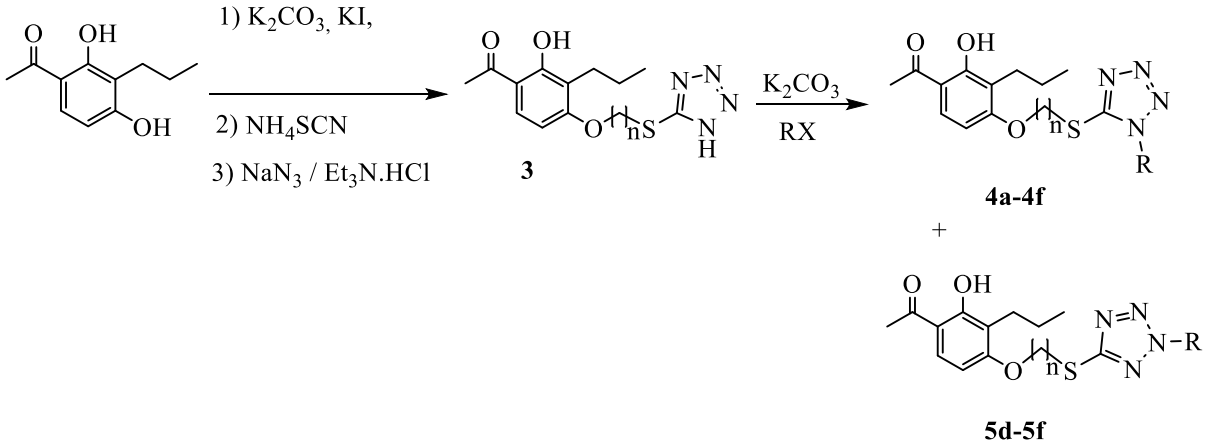
2.3. Antimicrobial Susceptibility Assay

The *in vitro* antimicrobial activities of the hydroxyacetophenone-thiotetrazole hybrids **4a-4f** and **5d-5f** were investigated against clinical isolates by the broth microdilution procedure suggested by EUCAST.[30-32] The MBC/MFC (Minimum Bactericidal/Fungicidal Concentration), and MIC (Minimum Inhibitory Concentration) of the compounds were determined. All isolates were obtained from the culture collection of Niğde Ömer Halisdemir University, Faculty of Medicine, Department of Medical Microbiology. Since the clinical isolates had originated from anonymized clinical samples obtained during routine laboratory procedures, patient consent and ethical approval were not considered necessary. The antibacterial activity tests were undertaken against Gram-negative bacteria (*Escherichia. coli*, *Pseudomonas aeruginosa* and *Stenotrophomonas maltophilia)* and Gram-positive bacteria (*Staphylococcus aureus* and *Staphylococcus epidermidis*). The antifungal activity measurements were performed against *Candida albicans*, and *Aspergillus fumigatus*. The reference antibacterial agents that were used in this study were imipenem, vancomycin, and gentamicin. The reference antifungal agent that was used in this study was fluconazole. The compounds were tested according to the procedure described in a previous study.[27]

3. Results and Discussion

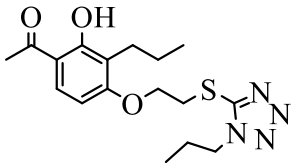
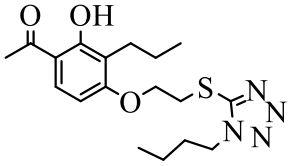
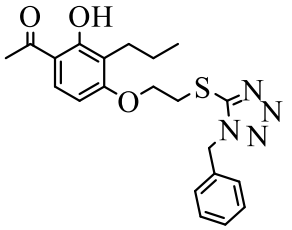
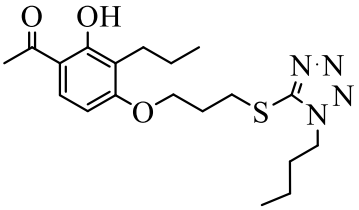
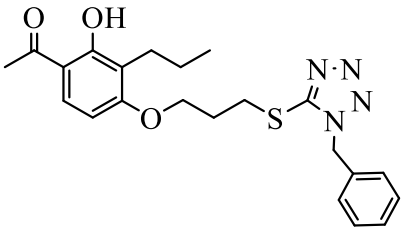
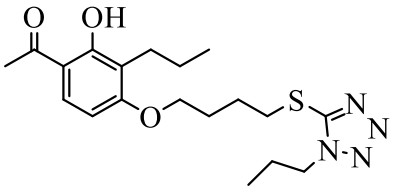
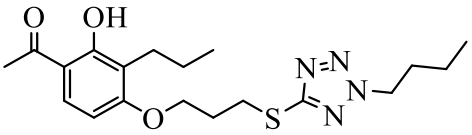
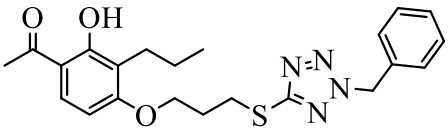
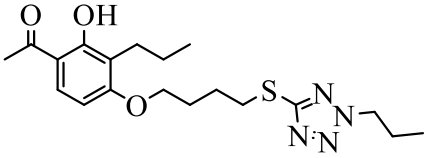
In this study, novel hybrid compounds in which 2′-hydroxyacetophenone and *N*-alkylated thiotetrazole pharmacophores were combined with methylene spacers, **4a-4f** and **5d-5f**, were synthesized. A four-step synthesis process was used to generate the hybrid compounds. The synthesis procedure of the target molecules is presented in Scheme 1.

1-[4-(3-((1*H*-tetrazol-5-yl)thio)alkoxy)-2-hydroxy-3-propylphenyl]ethanones (**3**) were synthesized by a method known in the relevant literature. [28,29] The structures of compounds **3** were confirmed by comparing their physical and spectral data to those that were previously reported.[28,29] To yield the target compounds, 1-[4-(3-((1*H*-tetrazol-5-yl)thio)alkoxy)-2-hydroxy-3-propylphenyl]ethanones were allowed to react with particular alkyl halides in the presence of potassium carbonate.[27] The chemical yields of the reactions were in the range of 40-77% (Table 1). The structures of **4a-4f** and **5d-5f** were estimated by FTIR, ^{1}H-NMR, ^{13}C-APT, and HRMS. All data confirmed the proposed structures. **4a-4f** and **5d-5f** were reported for the first time.



Scheme 1. Synthesis pathway of hydroxyacetophenone-tetrazole hybrids **4a-4f** and **5d-5f**

Table 1. The yields and HRMS analysis results of the compounds **4a-4f** and **5d-5f**

Compound	Molecular Structure	Yield	HRMS *m/z* [M+H]$^+$	
		%	Calculated	Found
4a		77	365.1647	365.1631
4b		74	379.1804	379.1782
4c		62	413.1647	413.1661
4d		55	393.1960	393.1944
4e		52	427.1804	427.1810
4f		58	393.1960	393.1953
5d		44	393.1960	393.1874
5e		47	427.1804	427.1711
5f		40	393.1960	393.1957

Hydroxyacetophenones have been documented as antibacterial agents.[9-13] According to findings obtained in previous studies, [11,13,33] the presence of acetyl and hydroxyl groups attached to the benzene ring is necessary for antimicrobial activity because these groups probably provide an appropriate balance between hydrophobicity and polarity, which is very important for the overall potency of the agent. However, antimicrobial activity varies depending on the binding sites of the hydroxyl groups in the molecule.

In this study, novel hybrid compounds (**4a-4f** and **5d-5f**) in which 2′-hydroxyacetophenone and *N*-alkylated thiotetrazole were combined with methylene spacers of different lengths were synthesized, and the antimicrobial activities of the synthesized compounds were investigated using the broth microdilution method. The antimicrobial activities of **4a-4f** (hydroxyacetophenones coupled to 1-alkyl-1*H*-thiotetrazole) and **5d-5f** (hydroxyacetophenones coupled to 2-alkyl-2*H*-thiotetrazole) were tested against clinical isolates of Gram-negative bacteria including *P. aeruginosa, S. maltophilia* and *E. coli*, Gram-positive bacteria including *S. epidermidis*, and *S. aureus*, and fungal species (*A. fumigatus*, and *C. albicans*). The MIC and MBC/MFC values are listed in Tables 2 and 3, respectively. Accordingly, compounds **4a-4f** and **5d-5f** showed a broad-spectrum antimicrobial activity against all strains that were tested in the study. Their activity was not limited to any particular group of microorganisms. All bacteria and fungi tested in this study were inhibited with MIC values ranging from 4 to128 µg/mL. Imipenem, vancomycin, and gentamicin showed antibacterial activity with MIC values ranging from 2 to16 µg/mL. Fluconazole showed antifungal activity with a MIC value of 32 µg/mL.

Table 2. Minimum inhibitory concentration (MIC) values of **4a-4f** and **5d-5f**

	MIC values (µg/mL)						
Compounds	***S. aureus***	***S. epidermidis***	***E. coli***	***P. aeruginosa***	***S. maltophilia***	***C. albicans***	***A. fumigatus***
4a	8	4	8	16	16	16	8
4b	128	64	64	32	64	32	16
4c	64	128	64	64	64	64	16
4d	128	64	64	64	64	16	16
4e	32	32	32	32	32	32	16
4f	64	64	64	32	64	32	16
5d	8	4	8	16	16	16	4
5e	32	32	32	32	32	32	16
5f	128	64	64	32	64	16	16
Gentamicin	2	4	4	8	4	-	-
Vancomycin	2	2	-	-	-	-	-
Imipenem	-	-	8	16	4	-	-
Fluconazole	-	-	-	-	-	32	32

4a and **5d** were the most active antibacterial members. Both had the same influence on the tested isolates. Their MIC values ranged from 4 to 16 µg/ml, and their MBC values ranged from 32 to 128 µg/mL. **4a** and **5d** also showed the same potency as the reference drug, imipenem, against *E. coli* and *P. aeruginosa* with MIC values of 8 and 16 µg/mL, respectively. These two compounds displayed the same efficacy as gentamicin against *S. epidermidis* with a MIC value of 4 µg/mL. However, the reference antibacterial agent vancomycin showed a much better antibacterial activity against *S. aureus* and *S. epidermidis* compared to **4a** and **5d**.

It was observed that the **4e** and **5e** isomers exhibited the same antimicrobial activity. The **4f** and **5f** tautomer pairs also showed the same bactericidal activity against all tested bacteria except for *S. aureus*. **4f** was twice as active against *S. aureus* as its 2*H*-tautomeric form, **5f**. On the other hand, the opposite was true for compounds **4d** and **5d**. **5d** was at least four times more potent than its 1*H*-tautomeric form, **4d**.

In a study on hydroxyacetophenones, 2′-hydroxy-3′,4′,6′-trimethoxyacetophenone inhibited *P. aeruginosa* and *S. aureus* with a MIC value of 128 µg/mL.[9] It is noteworthy that hydroxyacetophenone-

thiotetrazole hybrids (**4a-4f** and **5d-5f**) inhibited bacterial growth much more effectively than 2′-hydroxy-3′,4′,6′-trimethoxyacetophenone did against all tested strains. The incorporation of a tetrazole moiety into the hydroxyacetophenone substrate resulted in increased efficacy.

Last of all, if all *in vitro* antibacterial activity results are evaluated collectively, it can be stated, except for **4a** and **5d**, that the synthesized compounds had weak activities against the tested isolates compared to the reference antibacterial agents. In addition to their bacteriostatic effects, these compounds also exhibited varying levels of bactericidal activity against the tested isolates (Table 3 and Figure 4).

Table 3. Minimum bactericidal concentrations (MBC) and minimum fungicidal concentrations (MFC) values of **4a-4f** and **5d-5f**

	MBC/MFC values (µg/mL)						
Compounds	***S. aureus***	***S. epidermidis***	***E. coli***	***P. aeruginosa***	***S. maltophilia***	***C. albicans***	***A. fumigatus***
4a	64	64	128	64	32	32	64
4b	256	128	128	64	128	64	64
4c	128	>256	128	128	128	128	64
4d	>256	128	128	256	128	64	64
4e	128	128	128	128	64	64	64
4f	128	128	256	64	128	64	64
5d	64	64	128	64	32	32	32
5e	128	128	128	128	64	64	64
5f	128	128	128	64	128	32	64
Gentamicin	4	16	16	32	16	-	-
Vancomycin	16	8	-	-	-	-	-
Imipenem	-	-	32	32	8	-	-
Fluconazole	-	-	-	-	-	128	64

*****: No activity

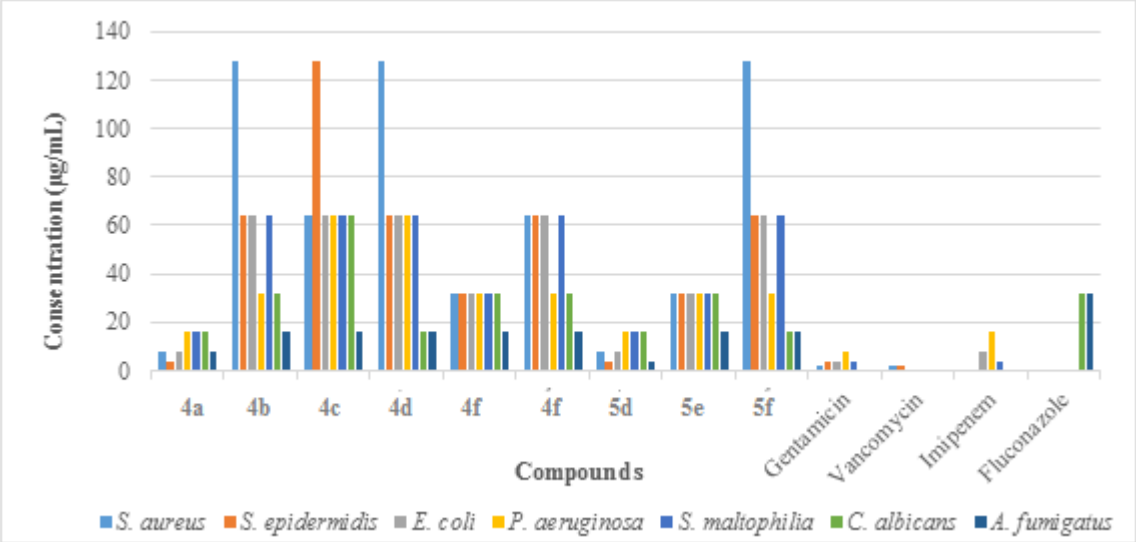


Figure 3. MIC values (µg/mL) of the synthesized compounds against tested isolates

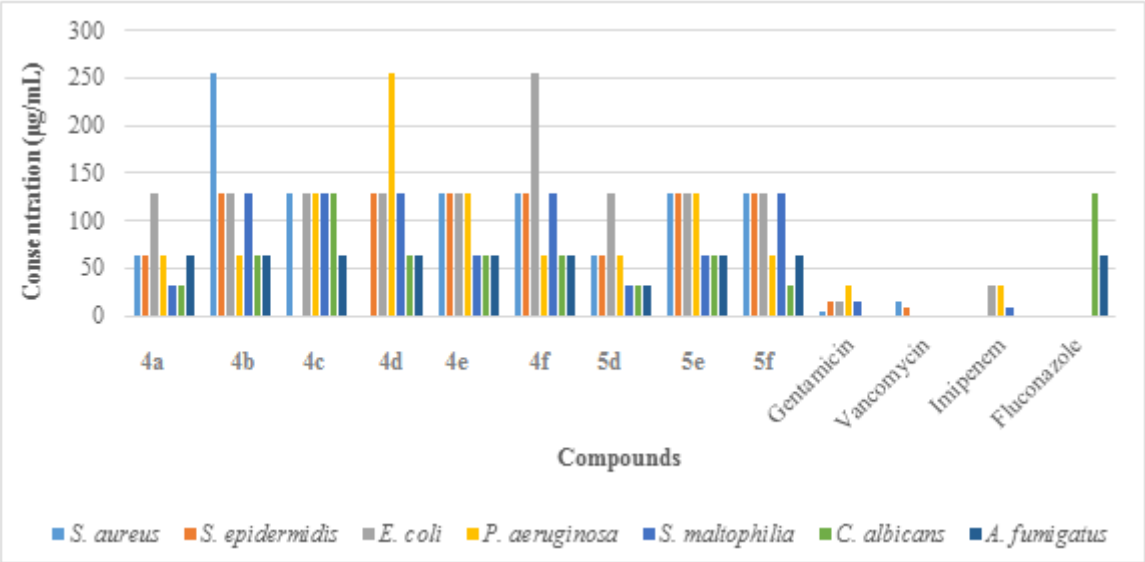


Figure 4. MBC/MFC values (µg/mL) of the synthesized compounds against tested isolates

The hydroxyacetophenone-thiotetrazole hybrids exhibited an antifungal activity against the tested fungal isolates with MIC values ranging from 4 to 64 µg/mL. They showed comparable or much higher antifungal activity against *C. albicans* and *A. fumigatus* than the reference drug, namely fluconazole (fluconazole MIC=32 µg/mL). It was found that the activities of the compounds against the *A. fumigatus* isolates were stronger than that of fluconazole. Their MIC values ranged from 4 to 16 µg/ml. **5d** and **4a** were the most active antifungal members with MIC values of 4 and 8 µg/mL, respectively. In fact, **5d** was found to have an eight times higher MIC value than that of fluconazole against *A. fumigatus* (MIC=4 µg/mL).

Simonsen et al. reported that 2′-hydroxy-4′,6′-dimethoxyacetophenone showed moderate antifungal activity against *C. albicans* with MIC>90 µg/mL.[7] In this study, **4a**-**4f** and **5d**-**5f** displayed antifungal activity against *C. albicans* with MIC values ranging from 16 to 64 µg/mL (MFCs 32-128 µg/mL). **4a**, **4d**, **5d**, and **5f** showed an antifungal activity against *C. albicans* that was one-fold higher than that of fluconazole with a MIC value of 16 µg/mL, while other compounds displayed the same and/or lower levels of activity compared to the reference antifungal agent (Table 2). In addition to their fungistatic effects, these compounds also exhibited different levels of fungicidal activity (Table 3 and Figure 4).

4. Conclusion

In this study, hydroxyacetophenone-thiotetrazole hybrids were synthesized and the antimicrobial activities of the hybrids were tested. In conclusion, all compounds exhibited significant activity and were found to inhibit all bacteria and fungi tested in the study. They showed a broad-spectrum antimicrobial activity against all strains that were tested in the study. In addition to their bacteriostatic and fungistatic effects, these compounds also exhibited varying levels of bactericidal and fungicidal activities against the tested isolates. **4a** and **5d** were the most active antibacterial members. We believe that the introduction of a tetrazole moiety into hydroxyacetophenone improves antimicrobial activity, and such a hybridization process has the potential to enhance inhibition. Based on the results of the study, we think most of the compounds (especially **4a** and **5d**) could be potent inhibitors against some Gram-positive bacteria, Gram-negative bacteria, and fungi, and they could be used as potential drugs for the prevention of infectious diseases in the future.

Supporting Information

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

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