Synthesis, antioxidant and antimicrobial properties of novel pyridyl-carbonyl thiazoles as dendrodoine analogs

Zafer ŞAHİN1*, Sevde Nur BİLTEKİN2, Leyla YURTTAŞ3, Şeref DEMİRAY AK1

1Department of Pharmaceutical Chemistry, School of Pharmacy, İstanbul Medipol University, İstanbul, Turkey
2Department of Pharmaceutical Microbiology, School of Pharmacy, İstanbul Medipol University, İstanbul, Turkey
3Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Anadolu University, Eskişehir, Turkey

* Correspondence: zsahin@medipol.edu.tr

Abstract: Marine compound dendrodoine was first obtained from tunicate species (Dendrodo grossularia). It has a five-membered ring, namely, it is a heterocycle thiadiazole, which is found rarely in natural sources. Following its biological activities, novel analogs have been investigated recently. Synthesis of the analogs for this study is realized with uncommon thiazole closure, including methylene-carbonyl condensation. Structures are elucidated by NMR (1H, 13C) and HRMS spectrums. As an alkaloid derivative, antioxidant properties were evaluated with DPPH and FRAP assays and antimicrobial effect with microdilution method. Among the series, 3bc-3cf showed higher antioxidant activity than those having 3 or 4-pyridyl substituents. There is lesser activity for 2-pyridyl for 2-pyridyl containing group, which may be a result of intramolecular interactions. No activity was observed against gram-negative bacteria at 250 μg/mL. 3ae and 3ce showed activity at 64 μg/mL against S. aureus and 3ae showed activity at 16 μg/mL against S. epidermidis gram-positive bacteria. Chloramphenicol showed activity against all microorganisms at 8–16 μg/mL. Sixteen original dendrodoine analogs have been defined by close/higher activity compared to dendrodoine analogs and Trolox.

Key words: Antioxidant, antimicrobial, thiazole, dendrodoine

1. Introduction

Marine tunicates are animals living in different deepness levels of oceans and are usually attached to docks. Dendrodoine is an alkaloid that was isolated from Dendroda grossularia indigenous in North Britain in 1980 [1]. Dendrodoine synthesis was accomplished 4 years after the first isolation. It has a thiadiazole ring which is rarely found in natural compounds, and it is known to be a part of functional synthetic compounds [2]. Beyond its unique thiadiazole ring, it is also a bioisoster of aminothiazoles. Aminothiazoles have a diverse biological spectrum including anticancer, antimicrobial, antioxidant, anti diabetic, anticonvulsant, antiinflammatory, antihypertensive, and protective activities. There are approved drugs, such as meloxicam, cefdinir, famotidine, bearing this moiety [3–5].

Aminothiazoles with lone pair electrons can be very dangerous if they are converted to reactive oxygen species. These reactive molecules can interact with cellular mechanisms. In biological mechanisms, O2 reduces to H2O via electron transfer pathways such as NADP/NADPH. And this process produces free-radicals (FRs) or reactive oxygen species (ROSs). [6]. FRs or ROSs have homeostatic functions at normal conditions and they are normally produced in small amounts; however, overexpression of them may propagate harmful chain reactions using DNA, RNA, proteins, and lipids as substrate. Finally, these reactions may be the cause of various pathogenic processes such as tumor growth and oxidative stress [7–9].

An analog synthesis is a functional approach in medicinal chemistry. In this respect, natural compounds have been extensively researched. There is only a few studies about dendrodoine analogs (Figure 1), and these studies are usually based on antioxidant activity [1,10-14].

In this study, we have synthesized trisubstituted aminothiazole compounds bearing pyridyl and phenyl groups and have evaluated their antioxidant and antimicrobial properties. DPPH free-radical scavenging and FRAP iron reducing properties were measured for antioxidant capacity. Besides, antimicrobial properties were evaluated against 8 gram-positive and gram-negative bacteria.

* Correspondence: zsahin@medipol.edu.tr

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2. Materials and methods

2.1. Synthesis

The reactants necessary for the synthesis process were purchased from Sigma-Aldrich Chemical Corp. Melting point of title molecules were accomplished by a Stuart melting point apparatus and experiments were performed in duplicate. $^1$H-NMR and $^{13}$C-NMR spectrums were recorded in Bruker 300 MHz UltraShield NMR and Bruker 75 MHz UltraShield NMR, respectively. DMSO-$d_6$ was used as solvent and TMS was used as standard. High resolution mass spectrums were recorded in Shimadzu 8040 LC/MS/MS ITTOF system with the electron spray method (ESI). IC$_{50}$ values of the title molecules were calculated using GraphPad Prism software version 7.02.

2.1.1. Synthesis of benzoyl thioureas (2a-f)

Ammonium thiocyanate (500 mmol) was dissolved in acetone. After it becomes a clear solution, 500 mmol benzoyl chloride was added to it quite slowly. The mixture became white blurry after 30 min. An equivalent mole of corresponding amine (500 mmol) was added. The mixture was then boiled for 6 h. The finalization of the process was decided with thin-layer chromatography using ethyl acetate 1:1 petroleum ether solvent system. Precipitation was filtered off, and mixed with water. The obtained solid material was recrystallized using ethyl alcohol [15].

2.1.2. Synthesis of 2-bromoacetylpyridines (1a-c)

Acetyl pyridine (250 mmol) was dissolved in chloroform. After 15 min stirring, 250 mmol bromine (diluted in chloroform) was added quite slowly to the mixture. It was checked with thin-layer chromatography that reaction ended, and then solid material was gathered on the bottom. Because of the basic nitrogen, each compound was formed as HBr salt. Compounds were used as HBr salt in the next step [16].

2.1.3. Synthesis of target compounds (3aa-af, 3ba-bf, 3cc-cf)

The target molecules were obtained using a distinct ring closure method including methylene-carbonyl condensation (Figure 2). During reactions, bromoacetylpyridines (1a-c) (20 mmol) and (2a-f) (20 mmol) were mixed and heated in ethyl alcohol. When it was certain that the reaction ended, the mixture was left for cooling (Table 1). When it reached 15–20 °C, it was poured into cold water (50 mL), and then it was added to water and neutralization was made using NaHCO$_3$. The final compounds were dissolved and recrystallized using ethyl alcohol [17-21].

### (2-(Dimethylamino)-4-phenylthiazol-5-yl)(pyridin-2-yl)methanone (3aa)

Yield: 82%. m.p.: 160–161 °C. $^1$H-NMR (300 MHz, DMSO-$d_6$, ppm) δ: 3.19 (6H, s, N(CH$_3$)$_2$), 7.25–7.32 (3H, m, Ar-H), 7.43–7.53 (3H, m, Ar-H), 7.83 (1H, d, $J$: 7.76 Hz, Ar-H), 7.91 (1H, dt, $J$: 8.58, 1.70 Hz, Ar-H), 8.52 (1H, d, $J$: 4.92 Hz, Ar-H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$, ppm) δ: 40.5 (N-CH$_3$), 116.3, 123.2, 126.8, 127.8, 128.8, 129.9, 136.9, 137.9, 148.2, 154.9 (thiazole C$_4$), 163.8 (pyridine C$_2$), 173.9 (thiazole C$_2$), 182.7 (C=O). HRMS (m/z): [M+H]$^+$ calcd for C$_{17}$H$_{15}$N$_3$OS: 310.1005; found: 310.1009.

### (2-(Diethylamino)-4-phenylthiazol-5-yl)(pyridin-2-yl)methanone (3ab)

Yield: 75%. m.p.: 112–114 °C. $^1$H-NMR (300 MHz, DMSO-$d_6$, ppm) δ: 1.22 (6H, t, $J$: 7.03 Hz, (CH$_2$)$_2$), 3.57 (4H, q, $J$: 7.06 Hz, N(CH$_2$)$_2$), 7.23–7.30 (3H, m, Ar-H), 7.42–7.49 (3H, m, Ar-H), 7.80–7.91 (2H, m, Ar-H), 8.48 (1H, d, $J$: 4.76 Hz, Ar-H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$, ppm) δ: 12.8 (CH$_3$), 48.8 (N-CH$_2$), 115.9, 123.3, 126.7, 127.3, 128.8, 128.9, 129.6, 129.9, 130.3, 130.8, 136.9, 137.8, 148.2, 155.1 (thiazole C$_4$), 163.7 (pyridine C$_2$), 172.3 (thiazole C$_2$), 182.9 (C=O). HRMS (m/z): [M+H]$^+$ calcd for C$_{19}$H$_{19}$N$_3$OS: 338.1314; found: 338.1322.

### (4-Phenyl-2-(pyrrolidin-1-yl)thiazol-5-yl)(pyridin-2-yl)methanone (3ac)

Yield: 70%. m.p.: 180–182 °C. $^1$H-NMR (300 MHz, DMSO-$d_6$, ppm) δ: 2.01 (4H, brs, (CH$_2$)$_2$), 3.51 (4H, brs, N(CH$_2$)$_2$), 7.27–7.32 (3H, m, Ar-H), 7.42–7.53 (3H, m, Ar-H), 7.81–7.91 (2H, m, Ar-H), 8.53 (1H, d, $J$: 4.66 Hz, Ar-H). $^{13}$C-NMR
Figure 2. Synthesis of the target compounds.

(75 MHz, DMSO-d$_6$, ppm) δ: 25.6 (CH$_3$), 49.9 (N-CH$_3$), 115.7, 123.2, 126.8, 127.8, 128.3, 128.7, 129.9, 137.1, 148.2, 155.0 (thiazole C$_x$), 164.1 (pyridine C$_y$), 170.5 (thiazole C$_z$), 182.5 (C=O). HRMS (m/z): [M+H]$^+$ calcd for C$_{30}$H$_{25}$N$_2$O$_3$: 336.1152; found: 336.1165.

(4-Phenyl-2-(piperidin-1-yl)thiazol-5-yl)(pyridin-2-yl)methanone (3ad)
Yield: 68%. m.p.: 124.5 °C. $^1$H-NMR (300 MHz, DMSO-d$_6$, ppm) δ: 1.63 (6H, brs, (CH$_3$)$_2$), 3.60 (4H, brs, N(CH$_3$)$_2$), 7.24–7.31 (3H, m, Ar-H), 7.44 (2H, d, J: 7.65 Hz, Ar-H), 7.47–7.52 (1H, m, Ar-H), 7.83 (1H, d, J: 7.58 Hz, Ar-H), 7.90 (1H, dt, J: 7.55, 1.67 Hz, Ar-H), 8.51 (1H, d, J: 4.81 Hz, Ar-H). $^{13}$C-NMR (75 MHz, DMSO-d$_6$, ppm) δ: 23.9 (CH$_3$), 49.2 (N-CH$_3$), 115.9, 123.3, 126.8, 127.8, 128.8, 129.9, 136.9, 137.9, 148.2, 154.9 (thiazole C$_x$), 163.7 (pyridine C$_y$), 173.6 (thiazole C$_z$), 182.8 (C=O). HRMS (m/z): [M+H]$^+$ calcd for C$_{36}$H$_{29}$N$_3$O$_3$: 350.1322; found: 350.1328.

(2-Azetan-1-yl)-4-phenylthiazol-5-yl(pyridin-2-yl)methanone (3ae)
Yield: 85%. m.p.: 127–129 °C. $^1$H-NMR (300 MHz, DMSO-d$_6$, ppm) δ: 1.55 (4H, brs, (CH$_3$)$_2$), 1.79 (4H, brs, (CH$_3$)$_2$), 3.66 (4H, brs, N(CH$_3$)$_2$), 7.22–7.33 (3H, m, Ar-H), 7.42–7.50 (3H, m, Ar-H), 7.82 (1H, d, J: 7.88 Hz, Ar-H), 7.89 (1H, dt, J: 7.50, 1.73 Hz, Ar-H), 8.49 (1H, d, J: 4.81 Hz, Ar-H). $^{13}$C-NMR (75 MHz, DMSO-d$_6$, ppm) δ: 27.5 (CH$_3$), 115.8, 123.2, 126.7, 127.8, 128.8, 129.9, 136.9, 137.8, 148.2, 155.1 (thiazole C$_x$), 163.7 (pyridine C$_y$), 173.1 (thiazole C$_z$), 182.7 (C=O). HRMS (m/z): [M+H]$^+$ calcd for C$_{22}$H$_{20}$N$_4$: 364.1480; found: 364.1478.

(2-Morpholin-4-phenylthiazol-5-yl)(pyridin-2-yl)methanone (3af)
Yield: 90%. m.p.: 149–151 °C. $^1$H-NMR (300 MHz, DMSO-d$_6$, ppm) δ: 3.60 (4H, t, J: 4.88 Hz, N(CH$_3$)$_2$), 3.74 (4H, t, J: 4.36 Hz, O(CH$_3$)$_2$), 7.25–7.33 (3H, m, Ar-H), 7.44 (2H, dd, J: 7.49, 1.92 Hz, Ar-H), 7.50–7.55 (1H, m, Ar), 7.86 (1H, td, J: 7.67, 1.22 Hz, Ar-H), 7.93 (1H, td, J: 7.84, 1.74 Hz, Ar-H), 8.53 (1H, d, J: 4.53 Hz, Ar-H). $^{13}$C-NMR (75 MHz, DMSO-d$_6$, ppm) δ: 48.1 (N-CH$_3$), 65.8 (CH$_2$-O), 116.2, 123.3, 127.01, 127.8, 128.9, 129.9, 136.7, 138.0, 148.2, 154.6 (thiazole C$_x$), 163.2 (pyridine C$_y$), 174.1 (thiazole C$_z$), 182.9 (C=O). HRMS (m/z): [M+H]$^+$ calcd for C$_{23}$H$_{22}$N$_4$O$_2$: 352.1160; found: 352.1114.

(2-(Dimethylamino)-4-phenylthiazol-5-yl)(pyridin-3-yl)methanone (3ba)
Yield: 68%. m.p.: 174–176 °C. $^1$H-NMR (300 MHz, DMSO-d$_6$, ppm) δ: 3.19 (6H, s, N(CH$_3$)$_2$), 7.05–7.17 (4H, m, Ar-H), 7.23–7.26 (2H, m, Ar-H), 7.83 (1H, td, J: 7.82, 2.02 Hz, Ar-H), 8.38–8.42 (1H, m, Ar-H), 8.52 (1H, d, J: 4.92 Hz, Ar-H). $^{13}$C-NMR (75 MHz, DMSO-d$_6$, ppm) δ: 40.3 (N-CH$_3$), 122.4, 123.2, 128.0, 128.3, 129.1, 129.2, 130.4, 134.6, 136.2, 149.4, 151.5 (thiazole C$_x$), 161.0 (pyridine C$_y$), 171.9 (thiazole C$_z$), 185.9 (C=O). HRMS (m/z): [M+H]$^+$ calcd for C$_{22}$H$_{19}$N$_3$O$_2$: 310.0998; found: 310.1009.

(2-(Diethylamino)-4-phenylthiazol-5-yl)(pyridin-3-yl)methanone (3bb)
Yield: 62%. m.p.: 143–144 °C. $^1$H-NMR (300 MHz, DMSO-d$_6$, ppm) δ: 1.23 (6H, t, J:6.90 Hz, (CH$_3$)$_2$), 3.58 (4H, q, J: 7.05 Hz, N(CH$_3$)$_2$), 7.05–7.11 (3H, m, Ar-H), 7.14–7.20 (1H, m, Ar-H), 7.23–7.26 (2H, m, Ar-H), 7.65 (1H, td, J: 8.06, 1.95 Hz, Ar-H), 8.38–8.42 (2H, m, Ar-H). $^{13}$C-NMR (75 MHz, DMSO-d$_6$, ppm) δ: 12.7 (CH$_3$), 46.0 (N-CH$_3$), 121.7, 123.1, 128.0, 128.3, 129.0, 129.2, 130.4, 134.7, 135.0, 136.1, 149.4, 151.5 (thiazole C$_x$), 161.1 (pyridine C$_y$), 170.4 (thiazole C$_z$), 185.8 (C=O). HRMS (m/z): [M+H]$^+$ calcd for C$_{22}$H$_{18}$N$_3$O$_2$: 338.1323; found: 338.1322.

(2-(Pyrrolidin-1-yl)-4-phenylthiazol-5-yl)(pyridin-3-yl)methanone (3bc)
Yield: 83%. m.p.: 176–177 °C. $^1$H-NMR (300 MHz, DMSO-d$_6$, ppm) δ: 2.02 (4H, brs, (CH$_3$)$_2$), 3.51 (4H, brs, N(CH$_3$)$_2$), 7.05–7.25 (6H, m, Ar-H), 7.64 (1H, td, J: 7.91, 2.09 Hz, Ar-H), 8.37–8.41 (2H, m, Ar-H). $^{13}$C-NMR (75 MHz, DMSO-d$_6$),
Table 1. R groups of the synthesized compounds.

| R₁ | R₂ | Isolated yield (%) | R₁ | R₂ | Isolated yield (%) |
|----|----|-------------------|----|----|-------------------|
| 3aa | 2-pyridyle | Dimethylamine | 82 | 3bc | 3-pyridyle | Pyrrolidine | 83 |
| 3ab | 2-pyridyle | Diethylamine | 75 | 3bd | 3-pyridyle | Piperidine | 66 |
| 3ac | 2-pyridyle | Piperidine | 70 | 3be | 3-pyridyle | Hexamethyamine | 70 |
| 3ad | 3-pyridyle | Dimethylamine | 68 | 3bf | 3-pyridyle | Morpholine | 84 |
| 3ae | 2-pyridyle | Hexamethyamine | 85 | 3cc | 4-pyridyle | Pyrrolidine | 76 |
| 3af | 3-pyridyle | Morpholine | 90 | 3cd | 4-pyridyle | Piperidine | 70 |
| 3ba | 3-pyridyle | Diethylamine | 68 | 3ce | 4-pyridyle | Hexamethyamine | 78 |
| 3bb | 3-pyridyle | Diethylamine | 62 | 3cf | 4-pyridyle | Morpholine | 69 |

ppm δ: 25.7 (CH₂), 50.2 (N-CH₂), 122.1, 123.1, 128.0, 128.3, 129.0, 129.2, 130.4, 134.7, 135.0, 136.1, 149.3, 151.5 (thiazole C₄), 161.3 (pyridine C₄), 168.3 (thiazole C₅), 185.85 (C=O). HRMS (m/z): [M+H]⁺ calcd for C₁₉H₁₇N₃O: 336.1151; found: 336.1165.

(4-Phenyl-2-(piperidin-1-yl)thiazol-5-yl)(pyridin-3-yl)methanone (3bd)
Yield: 66%. m.p.: 143–145 °C. ¹H NMR (300 MHz, DMSO-d₆, ppm) δ: 1.64 (6H, brs, (CH₂)₃), 3.62 (4H, brs, N(CH₂)₂), 7.04–7.20 (4H, m, Ar-H), 7.22–7.25 (2H, m, Ar-H), 7.66 (1H, td, J: 7.98, 2.07 Hz, Ar-H), 8.38–8.42 (2H, m, Ar-H). ¹³C NMR (75 MHz, DMSO-d₆, ppm) δ: 25.3 (CH₂), 49.4 (N-CH₂), 121.8, 123.2, 128.0, 129.2, 130.3, 134.6, 136.2, 149.4, 151.6 (thiazole C₄), 161.0 (pyridine C₄), 171.5 (thiazole C₅), 186.0 (C=O). HRMS (m/z): [M+H]⁺ calcd for C₂₀H₁₉N₃O: 350.1322; found: 350.1320.

(2-Azepan-1-yl)-4-phenylthiazol-5-yl)(pyridin-3-yl)methanone (3be)
Yield: 70%. m.p.: 130–132 °C. ¹H NMR (300 MHz, DMSO-d₆, ppm) δ: 1.56 (4H, brs, (CH₂)₂), 1.80 (4H, brs, (CH₂)₂), 3.66 (4H, brs, N(CH₂)₂), 7.05–7.17 (4H, m, Ar-H), 7.23–7.25 (2H, m, Ar-H), 7.65 (1H, td, J: 7.84 Hz, 1.78 Hz, Ar-H), 8.37–8.42 (2H, m, Ar-H). ¹³C NMR (75 MHz, DMSO-d₆, ppm) δ: 27.5 (CH₂), 121.7, 123.1, 128.0, 129.2, 130.4, 134.7, 135.0, 136.1, 149.4, 151.5 (thiazole C₄), 161.1 (pyridine C₄), 171.2 (thiazole C₅), 185.8 (C=O). HRMS (m/z): [M+H]⁺ calcd for C₂₁H₂₁N₃O: 364.1480; found: 364.1478.

(2-Morpholino-4-phenylthiazol-5-yl)(pyridin-3-yl)methanone (3bf)
Yield: 84%. m.p.: 146–149 °C. ¹H NMR (300 MHz, DMSO-d₆, ppm) δ: 3.61 (4H, t, J: 4.37 Hz, N(CH₂)₂), 3.74 (4H, t, J: 4.37 Hz, O(CH₂)₂), 7.06–7.18 (4H, m, Ar-H), 7.23–7.26 (2H, m, Ar-H), 7.68 (1H, td, J: 7.98 Hz, 2.06 Hz, Ar-H), 8.39–8.44 (2H, m, Ar-H). ¹³C NMR (75 MHz, DMSO-d₆, ppm) δ: 48.2 (N-CH₂), 65.8 (CH₂-O), 122.4, 123.2, 128.1, 129.3, 130.4, 134.4, 134.8, 143.6, 149.5, 151.7 (thiazole C₄), 160.4 (pyridine C₄), 172.0 (thiazole C₅), 186.3 (C=O). HRMS (m/z): [M+H]⁺ calcd for C₁₉H₁₇N₃O₂: 352.1113; found: 352.1114.
(2-(Azepan-1-yl)-4-phenylthiazol-5-yl)(pyridin-4-yl)methanone (3ce)

Yield: 69%. m.p.: 171–172 °C. \(^{1}H\)-NMR (300 MHz, DMSO-\(d_6\), ppm) \(\delta\): 3.62 (4H, t, J: 4.23 Hz, N(CH\(_3\)))

(2-Morpholino-4-phenylthiazol-5-yl)(pyridin-4-yl)methanone (3cf)

Yield: 69%. m.p.: 171–172 °C. \(^{1}H\)-NMR (300 MHz, DMSO-\(d_6\), ppm) \(\delta\): 3.62 (4H, t, J: 4.23 Hz, N(CH\(_3\)))

2.2.1. DPPH radical scavenging assay

2,2-diphenyl-1-picrylhydrazyl (DPPH) sweep test was used for one type of antioxidant activity as reported by Lu et al. [22]. DPPH has a strong absorbance at 517 nm. DPPH starts to react by existence of a hydrogen donor (free-radical scavenger/antioxidant). The color change depends on the number of electrons captured and is determined with spectrophotometric measurement. Compounds and standard gallic acid were prepared in the concentration from 1.25 \(\mu\)M to 25 \(\mu\)M. These, in six different concentrations (1.25 \(\mu\)M, 2.5 \(\mu\)M, 5 \(\mu\)M, 10 \(\mu\)M, 12.5 \(\mu\)M, 25 \(\mu\)M), were added to 190 \(\mu\)L of simultaneously made solution of DPPH (0.1 mM in methanol). The reaction blend was kept in darkness for 40 min, and then the optical density was measured against the blank at 517 nm. The capability of the compounds of scavenging the DPPH radical was calculated as percent inhibition (%).

Here Ac is the absorbance of the control and At is the absorbance of the compounds; DPPH radical scavenging activity (%) = [(Ac – At)/Ac] \times 100. After the concentration calculations, IC\(_{50}\) values of each compound were calculated using GraphPad Prism. The results were calculated by comparison with the standard antioxidants, gallic acid and ascorbic acid. The assay was carried out in triplicate [22].

2.2.2. Ferric reducing antioxidant power (FRAP assay)

FRAP test was performed with the method of Benzie and Strain’s (1996) with some modifications [23,24]. To prepare FRAP freshly just before use, 300 mM acetate buffer (pH 3.6), 10 mM TPTZ solution (10 mM TPTZ in 40 mM HCl), and 20 mM FeCl\(_3\), \(6\)H\(_2\)O in a 10:1:1 ratio were mixed. Ten-microliter compounds of different concentrations (0.312 \(\mu\)M, 0.625 \(\mu\)M, 1.25 \(\mu\)M, 2.5 \(\mu\)M, 5 \(\mu\)M, 10 \(\mu\)M, 12.5 \(\mu\)M, 25 \(\mu\)M) were added to 190 \(\mu\)L of simultaneously made solution of DPPH (0.1 mM in methanol). The reaction blend was kept in darkness for 40 min, and then the optical density was measured against the blank at 517 nm. The capability of the compounds of scavenging the DPPH radical was calculated as percent inhibition (%).
shifted hydrogen is the one on the neighborhood of pyridine nitrogen. These hydrogens were observed between 8.29 and 8.53 ppm. In 13C NMR, carbonyl peaks were specifically observed approximately at 180 ppm. Following that, 2nd position of thiazole carbon was observed around 170 ppm. The 2nd position of pyridine and 4th position of thiazole were the following peaks for all compounds in descending order. Methyl or ethyl groups in the neighborhood of amine were recorded at 40 and 52 ppm, respectively. Other aliphatic carbons were recorded at 12 and 27 ppm, which represents methyl and ethyl groups on the amine, but not directly bound to nitrogen, respectively. HRMS results satisfied the molecular weights with high accuracy.

3.2. Antioxidant activity
Antioxidant activity was performed by two different common methods namely DPPH radical scavenging and ferric reducing ability (FRAP). DPPH activity was measured as IC50 values with mM unit whereas FRAP results are presented as Trolox equivalent antioxidant capacity (TEAC). The higher TEAC result means the higher antioxidant capacity.

In DPPH scavenging activity, 2-pyridyl derivatives (3aa-af) showed up to 65 mM IC50 value, except 3ad. Remarkably, 3 and 4-pyridyl derivatives showed less than 38 mM IC50, except for 3ba and 3bb. In terms of scavenging activity, standard ascorbic acid exhibited 3 mM. The most active compounds in the series were 3cf and 3bd with 28.10 and 26.02 mM, respectively (Table 2).

In FRAP reducing ability, experiments were performed at 5 μM concentrations. To examine the results, compounds showed a narrow range between 90.34 and 137.43 as TEAC. These results are approximately the quarter of gallic acid results on the same assay. In summary, compounds did not show higher or equal activity to standards (Table 2); however, they still have antioxidant capacity as novel chemicals.

3.3. Antimicrobial activity
Final compounds were examined for antibacterial properties on 8 microbial strains (Table 3). The results were presented as MIC (μg/mL) values. According to the results, there is not a considerable activity for gram-negative bacteria E. coli, P. aeruginosa, and K. pneumoniae. Compound 3ae (128 μg/mL) was the only compound that showed more than 256 μg/mL activity against these strains. As for gram-positive bacteria, 3ae, 3af, 3cc, 3cd, 3ce, and 3cf exhibited ≥128 μg/mL activity against different strains. Specifically, 3ae and 3ce showed 64 μg/mL activity against S. aureus. 3ae also exhibited 16 μg/mL activity against S. epidermidis. Chloramphenicol was used as a wide-spectrum standard and sulfamethoxazole was used as sulfanamide standard. Chloramphenicol showed 8–16 μg/mL activity against all bacteria as expected. Considerably, its MIC value is not too far from the results of 3ae. Sulfamethoxazole was not effective against gram-positive bacteria except for S. aureus (64 μg/mL). However, it showed high effect against E. coli (8 μg/mL) and P. aeruginosa (32 μg/mL) gram-negative bacteria.

4. Discussion
Synthesis of sixteen compounds was accomplished. In thiazole synthesis, ring closure is accomplished by methylene-carbonyl condensation. This process runs when there is carbonyl attached to thioamide moiety, unlike in the Hantzsch method. In this way, it is possible to synthesize trisubstituted thiazoles. In this method, sulfur basically attacks alkyl halide (CH2-Br) at the first stage and then bromine leaves the structure, prompting nucleophilic substitution. In the final step, the methylene, which stands between the carbonyl and the sulfur, forms a condensation and water withdrawal with the carbonyl arising from the thioamide moiety (Figure 2) [17–21].

Oceans are rich in many living organisms, including truncates and they have many different biologically active compounds. Antioxidant activity is one of the most important of those activities and compounds IC50 values are reported to be between 26.02 and 150.74 mM in DPPH test. 3 and 4-pyridyl derivatives showed higher activity compared to 2-pyridyls. Compounds 3ba and 3bb showed less activity compared to the rest of 3 and 4-pyridyl derivatives (3g-p). This can be interpreted as that the cyclic amine substituents is preferable, not alkyl amines (3ba, 3bb). Standard ascorbic acid was measured as 3.21 mM and this activity seems 9 times of our most active compound. However, in another study, the IC50 value of ascorbic acid was reported as 38.78 mM [27]. Trolox equivalent antioxidant capacity for FRAP assay was measured between 90.34 and 137.43, where gallic acid TEAC value was 476.8 and caffeic acid was 272 [28]. Synthesized compounds have antioxidant capacity approximately half of the standard caffeic acid and ¼ of gallic acid. According to antioxidant activity results, compounds have considerable antioxidant capacity but not equal to or higher than standard strong antioxidants such as ascorbic acid, gallic acid, and caffeic acid. DPPH results were measured between 1.25 μM and 25 μM concentrations. Interestingly, dendrodoine analog (Figure 1) was found 16.66 times less active compared to Trolox (measured at 12.28 μM [12]) whereas 3cf (IC50 26.02 μM) had close or higher activity to Trolox (Reported in the literature: 15–52 μM) [29,30]. In this respect, our compounds seem more active than dendrodoine analogs with respect to antioxidant results and have a close activity to Trolox compared to the literature results. Examining the antimicrobial...
results, compounds do not have significant antimicrobial activity except for 3ae. As a result, 16 dendrodoine analogs have been defined successfully with their antioxidant and antimicrobial properties.

**Conflict of interest**
The authors declare that there is no conflict of interest.
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