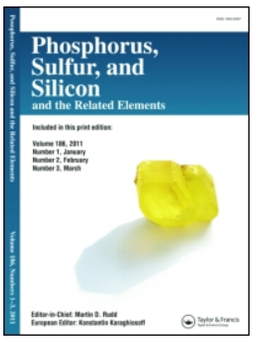

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New nalidixic acid–1,3-thiazolidin-4-one hybrids: Design, synthesis and *in vitro* antimicrobial activity

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ABSTRACT

In this paper, 14 new nalidixic acid–1,3-thiazolidin-4-one hybrid compounds (**17**–**30**) were synthesized by the cyclization reaction of corresponding *N*-substituted nalidixic acid hydrazones (**3**–**16**) with mercaptoacetic acid in the presence of 1,4-dioxane. The structures of the obtained compounds were confirmed by means of ^{1}H NMR and ^{13}C NMR spectroscopy. All newly synthesized hybrids were screened *in vitro* for antimicrobial activity. The antimicrobial activity assay indicated that compounds **17–30** showed good to moderate antimicrobial activity, especially against Gram-positive bacteria. Moreover, compound **29** inhibited growth of reference strains of Gram-negative bacteria belonging to *Enterobacteriaceae* family.

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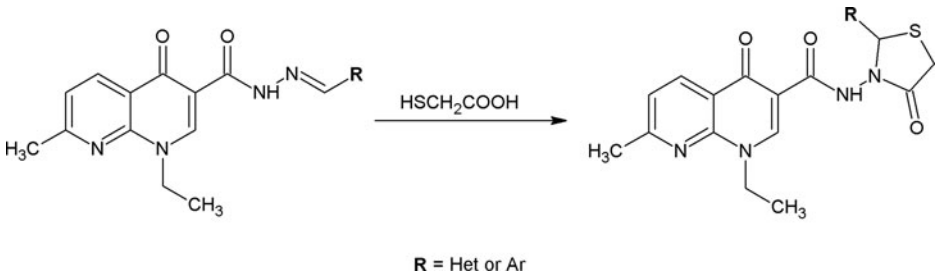
1,3-Thiazolidin-4-one derivatives; antimicrobial activity; MIC; MBC; nalidixic acid

GRAPHICAL ABSTRACT



Introduction

The introduction of nalidixic acid for the treatment of bacterial infections has begun the era of antibiotics collectively known as quinolones[1,2]. Quinolone antibiotics are still important as anti-infective agents and are widely prescribed for various infections[3]. Their activity is connected with the inhibition of bacterial DNA gyrase/topoisomerase IV system[3–5].

Our recent review and literature findings concerning the impact of modifying the chemical structure of nalidixic acid on antimicrobial activity indicated and confirmed that the carboxylic acid group at C-3 position is essential for antibacterial activity[6–9]. In an earlier paper, we synthesized new nalidixic acid hydrazones and screened them for *in vitro* antimicrobial activity[10]. In this paper, we decided to modify the structure of nalidixic acid by combining it with substituted 1,3-thiazolidin-4-one derivatives using the previously obtained hydrazones[10].

The 1,3-thiazolidin-4-one derivatives are interesting group of compounds exhibiting significant antibacterial activity[11,12] due to the interaction with MurB enzyme which inhibits the biosynthesis of the peptidoglycan—a polymer essential for cell wall of bacteria[13–15]. The 1,3-thiazolidin-4-one derivatives also show other interesting activities such as: anticonvulsant,[16] anticancer[17,18] and antiviral activity[19].

Based on the facts mentioned above in this paper, we would like to report the synthesis, spectral characterization, and *in vitro* antimicrobial study of new nalidixic acid–1,3-thiazolidin-4-one hybrids.

Results and discussion

Chemistry

New derivatives of nalidixic acid were obtained in a three-step synthesis. First, nalidixic acid hydrazide (**2**) was obtained by the reaction of nalidixic acid methyl ester (**1**) with 100% hydrazide hydrate. This reaction was conducted according to the procedure described earlier[10,20]. Then nalidixic acid

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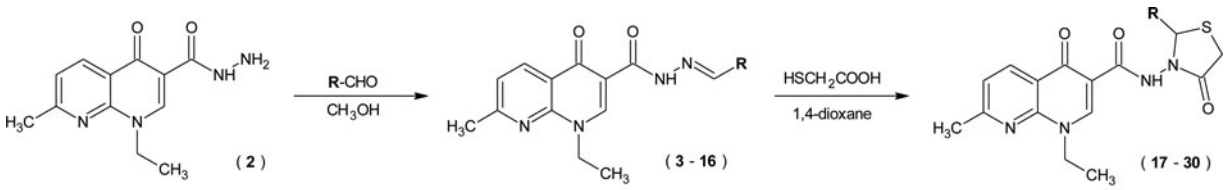

3, 17: R = 3-Br,4-OHC$_6$H$_3$
4, 18: R = 2-OH,5-BrC$_6$H$_3$
5, 19: R = 3-OEt,4-OHC$_6$H$_3$
6, 20: R = 4-OMeC$_6$H$_4$
7, 21: R = 2,3-(OMe)$_2$C$_6$H$_3$
8, 22: R = 3-Br-4-OMeC$_6$H$_3$
9, 23: R = 2-Cl-3-OMeC$_6$H$_3$
10, 24: R = 2-Br-5-FC$_6$H$_3$
11, 25: R = 2-Cl-6-FC$_6$H$_3$
12, 26: R = 2,3-F$_2$C$_6$H$_3$
13, 27: R = 2-pyrrolyl
14, 28: R = 5-Cl-2-furanyl
15, 29: R = 3-indolyl
16, 30: R = 6-Cl-5-benzo[1,3]dioxolyl

Scheme 1. Synthetic route to new nalidixic acid–1,3-thiazolidin-4-one hybrids (**17**–**30**).

hydrazones were synthesized by the condensation reaction of nalidixic acid hydrazide with corresponding substituted (hetero)aromatic aldehydes. This reaction was performed according to the procedure reported earlier by our group[10]. Finally, new hybrid compounds were prepared by the cyclization of *N*-substituted nalidixic acid hydrazones (**3–16**) with mercaptoacetic acid. This reaction begins by nucleophilic attack of anion of mercaptoacetic acid upon the carbon atom of hydrazone, followed by the capture of proton by nitrogen and subsequent cyclization with removal of water molecule[15]. All nalidixic acid hybrid derivatives (**17–30**) are new and their synthesis and structures are presented for the first time in the literature.

The ^{1}H NMR spectra of compounds (**17**–**30**) showed following signals corresponding to the specific group in 1,3-thiazolidin-4-one ring. The NH group gave a typical singlet signal in the range of δ 11.25–11.94 ppm, the singlet signals for CH_2 and CH groups were found in the range of δ 3.37–3.86 ppm and δ 5.25–6.51 ppm, respectively. In the ^{13}C NMR spectra of compounds (**17**–**30**), signals for CH_2 and CH groups for the thiazolidine system appeared in the range of δ 31.9–33.5 ppm and δ 60.9–67.9 ppm, respectively. The signal for C=O group was observed at δ 171.1–174.5 ppm. All other aliphatic and aromatic signals were found at usual regions. Based on the obtained spectral data, we successfully confirmed the formation of the expected hybrid compounds (**17**–**30**). The hybrid derivatives (**17–30**) were synthesized according to the reactions presented in Scheme 1.

The synthesized compounds (**17–30**) were *in vitro* screened for antibacterial and antifungal activity.

Microbiology

The results of our antimicrobial activity study indicated that all synthesized substances had no inhibitory effect on the growth of reference strains of yeasts *Candida* spp. However, our assays showed that the tested compounds exhibited some influence on the growth of reference strains of bacteria. Detailed results and discussion of antimicrobial screening together with the table (Table S1) with the activity data of compounds **17–30** expressed as MIC (μg/mL) against the reference strains of bacteria are presented in Supplemental Materials.

Experimental

Chemistry

All chemicals and solvents used in this study were purchased from Sigma-Aldrich (Munich, Germany) and Merck Co. (Darmstadt, Germany). Melting points are uncorrected and were marked with Fisher-Johns blocks (Fisher Scientific, Germany). The ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 300 apparatus (Bruker BioSpin GmbH, Germany) in DMSO-d_6 with TMS as internal standard. The chemical shifts are given in δ (ppm) scale using TMS as the standard reference. The coupling constants (*J*) are given in Hertz. The progress of the reaction and purity of obtained compounds were monitored by TLC on precoated aluminum sheets 60 F254 plates (Merck Co., USA), in a $CHCl_3/C_2H_5OH$ (10:1, v/v) solvent system. The spots were detected by exposure to a UV lamp at 254 nm. Elemental analysis of synthesized compounds was performed on AMZ 851 CHX analyser (PG, Gdańsk, Poland). The results of elemental analysis (C, H, N) were within ±0.4% of the calculated values.

Synthesis of nalidixic acid hydrazide (2)

The compound was prepared according to a literature procedure[10,20]. Analytical and spectral data were consistent with those reported in the literature[10].

Synthesis of nalidixic acid hydrazones (3–16)

Compounds (**3–16**) were prepared according to a literature procedure reported earlier by our group[10]. Compound **2** (2.46 g, 10 mmol) was dissolved in methanol (15 mL). The mixture was stirred until a clear solution was obtained. After that, the appropriate (hetero)aromatic aldehydes were added (11 mmol) and the solution was stirred at room temperature for 3 h. The precipitate obtained was filtered off, dried, and recrystallized from ethanol.

The analytical and spectral data of compounds (**3–16**) were reported earlier[10].

Synthesis of hybrid compounds (17–30)

To a solution of the corresponding nalidixic acid hydrazones **3–16** (10 mmol) in 1,4-dioxane (15 mL), mercaptoacetic acid

(0.92 g, 10 mmol) was slowly added. The mixture was stirred and heated under reflux for 12–24 h. Subsequently, the solvent was removed under reduced pressure and after that a 10% aquous solution of sodium bicarbonate (20 mL) was added. The precipitate formed was filtered off, dried, and purified by recrystallization from ethanol.

N-[2-(3-bromo-4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (17). Yield: 70%; m.p.: 148–150°C. Time of reaction: 24h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.38–1.43 (t, J = 6 Hz, J = 9 Hz, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.57 (s, 2H, CH_2), 4.58–4.65 (q, J = 6 Hz, J = 9 Hz, 2H, CH_2), 5.83 (s, 1H, CH), 6.92–6.95 (d, J = 9 Hz, 1H, ArH,), 7.20–7.33 (m, 1H, ArH), 7.47–7.49 (m, 1H, ArH), 7.51–7.54 (m, J = 9 Hz, 1H, ArH), 8.58–8.61 (d, J = 9 Hz, 1H, ArH), 9.05 (s, 1H, ArH), 10.90 (s, 1H, OH), 11.25 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.4 (CH_3), 24.3 (CH_3), 33.3 (CH_2), 45.5 (CH_2), 67.9 (CH), 105.0, 107.4, 115.3, 119.3, 121.9, 126.6, 134.2, 145.8, 156.4, 159.0, 160.5 (13C_{ar}), 163.4 (C=O), 172.4 (C=O), 180.1 (C=O). Analysis for $C_{21}H_{19}BrN_4O_4S$ (503.37) Calculated: C: 50.11%, H: 3.80%, N: 11.13%; Found: C: 50.16%, H: 3.76%, N: 11.16%.

N-[2-(5-bromo-2-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (18). Yield: 65%; m.p.: 205–207°C. Time of reaction: 24h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.38–1.43 (t, J = 6 Hz, J = 9 Hz, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.57 (s, 2H, CH_2), 4.58–4.65 (q, J = 6 Hz, J = 9 Hz 2H, CH_2), 5.57 (s, 1H, CH), 6.90–6.93 (d, J = 9 Hz, 1H, ArH), 7.27–7.32 (m, 1H, ArH), 7.39–7.40 (d, J = 3 Hz, 1H, ArH), 7.45–7.54 (m, 1H, ArH), 8.53–8.61 (m, 1H, ArH,), 9.03 (s, 1H, ArH), 10.94 (s, 1H, OH), 11.38 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.2 (CH_3), 24.2 (CH_3), 33.2 (CH_2), 45.5 (CH_2), 61.8 (CH), 105.3, 110.9, 118.8, 119.3, 121.9, 124.9, 129.9, 130.8, 137.3, 145.8, 150.1, 159.1, 160.6 (13C_{ar}), 160.3 (C=O), 171.1 (C=O), 180.1 (C=O). Analysis for $C_{21}H_{19}BrN_4O_4S$ (503.37) Calculated: C: 50.11%, H: 3.80%, N: 11.13%; Found: C: 50.09%, H: 3.85%, N: 11.15%.

N-[2-(3-ethoxy-4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (19). Yield: 75%; m.p.: 219–221°C. Time of reaction: 16h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.17–1.21 (t, J = 6 Hz, 3H, CH_3), 1.38–1.42 (t, 3H, CH_3, J = 6 Hz), 2.59 (s, 3H, CH_3), 3.39 (s, 2H, CH_2), 3.94–4.00 (q, J = 6 Hz, 2H, CH_2), 4.29–4.35 (q, J = 6 Hz, 2H, CH_2), 5.75 (s, 1H, CH), 6.56–6.58 (d, J = 6 Hz, 1H, ArH), 6.74–6.81 (m, 2H, ArH), 7.09–7.11 (d, J = 6 Hz, 1H, ArH), 8.15–8.17 (d, J = 6 Hz, 1H, ArH), 8.37 (s, 1H, ArH), 10.63 (s, 1H, OH), 11.54 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.4 (CH_3), 13.8 (CH_3), 24.3 (CH_3), 33.3 (CH_2), 45.7 (CH_2), 64.5 (CH_2), 67.9 (CH), 105.1, 111.8, 117.1, 117.8, 119.3, 121.9, 132.3, 137.3, 145.5, 145.8, 147.2, 159.1, 160.7 (13C_{ar}), 163.7 (C=O), 172.3 (C=O), 180.6 (C=O). Analysis for $C_{23}H_{24}N_4O_5S$ (468.52) Calculated: C: 58.96%, H: 5.16%, N: 11.96%; Found: C: 58.92%, H: 5.14%, N: 11.94%.

N-[2-(4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (20). Yield: 69%; m.p.: 229–231°C. Time of reaction: 16h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.38–1.43 (t, J = 6 Hz, J = 9 Hz, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.57 (s, 3H, CH_3), 3.74 (s, 2H, CH_2), 4.57–4.65 (q, J = 9 Hz, 2H, CH_2), 5.97 (s, 1H, CH), 6.92–6.95 (d, J = 9 Hz, 1H, ArH), 7.40–7.43 (d, J = 9 Hz, 1H, ArH), 7.47–7.49 (d, J = 6 Hz, 1H, ArH), 7.51–7.54 (d, J = 9 Hz, 1H, ArH), 8.47–8.50 (d, J = 9 Hz, 1H, ArH), 8.55 (s, 1H, ArH), 8.58–8.61 (d, J = 9 Hz, 1H, ArH), 11.25 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.4 (CH_3), 24.3 (CH_3), 33.5 (CH_2), 45.8 (CH_2), 56.0 (CH_3), 67.6 (CH), 105.1, 114.0, 119.3, 121.9, 126.7, 135.5, 137.3, 145.8, 159.8, 160.8, 161.8 (13C_{ar}), 163.8 (C=O), 172.4 (C=O), 180.6 (C=O). Analysis for $C_{22}H_{22}N_4O_4S$ (438.49) Calculated: C: 60.26%, H: 5.06%, N: 12.78%; Found: C: 60.31%, H: 5.08%, N: 12.76%.

N-[2-(2,3-dimethoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (21). Yield: 76%; m.p.: 222–224°C. Time of reaction: 16h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.35–1.37 (t, J = 6 Hz, 3H, CH_3), 2.66 (s, 3H, CH_3), 3.55 (s, 2H, CH_2), 3.71 (s, 3H, CH_3), 3.76 (s, 3H, CH_3), 4.54–4.62 (q, J = 6 Hz, J = 9 Hz, 2H, CH_2), 6.22 (s, 1H, CH), 7.05–7.14 (dd, J = 6 Hz, 2H, ArH), 7.47–7.50 (d, J = 9 Hz, 1H, ArH), 8.50–8.54 (d, J = 12 Hz, 1H, ArH), 8.59–8.62 (d, J = 9 Hz, 1H, ArH), 9.01 (s, 1H, ArH), 11.39 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.4 (CH_3), 24.3 (CH_3), 33.3 (CH_2), 45.8 (CH_2), 56.8 (CH_3), 60.6 (CH_3), 62.1 (CH), 105.1, 115.6, 119.3, 119.9, 121.6, 121.9, 127.7, 137.3, 144.1, 145.8, 151.8, 159.9, 160.7 (13C_{ar}), 163.8 (C=O), 172.3 (C=O), 180.6 (C=O). Analysis for $C_{23}H_{24}N_4O_5S$ (468.52) Calculated: C: 58.96%, H: 5.16%, N: 11.96%; Found: C: 58.91%, H: 5.14%, N: 11.99%.

N-[2-(3-bromo-4-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (22). Yield: 75%; m.p.: 124–126°C. Time of reaction: 20h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.38–1.42 (t, J = 6 Hz, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.85 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 4.57–4.63 (q, J = 6 Hz, 2H, CH_2), 5.25 (s, 1H, CH), 7.09–7.12 (d, J = 9 Hz, 1H, ArH), 7.21–7.24 (d, J = 9 Hz, 1H, ArH), 7.37–7.40 (dd, J = 3 Hz, 1H, ArH), 7.47–7.57 (m, 2H, ArH), 7.73–7.76 (dd, J = 3 Hz, 1H, ArH), 11.27 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.5 (CH_3), 24.2 (CH_2), 33.4 (CH_2), 45.8 (CH_2), 56.9 (CH_3), 67.9 (CH), 106.1, 111.3, 112.7, 119.3, 121.9, 125.8, 135.0, 136.4, 137.3, 145.8, 159.9, 160.75, 161.2 (13C_{ar}), 163.8 (C=O), 172.3 (C=O), 180.6 (C=O). Analysis for $C_{22}H_{21}BrN_4O_4S$ (517.39) Calculated: C: 51.07%, H: 4.09%, N: 10.83%; Found: C: 51.11%, H: 4.07%, N: 10.84%.

N-[2-(2-chloro-3-methoxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (23). Yield: 63%; m.p.: 237–239°C. Time of reaction: 12h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.36–1.40 (t, J = 6 Hz, 3H, CH_3), 3.57 (s, 2H, CH_2), 3.84 (s, 3H, CH_3), 3.88 (s, 3H, CH_3), 4.56–4.62 (q, J = 6 Hz, 2H, CH_2), 6.32 (s,

1H, CH), 6.73–6.75 (d, $J = 6$ Hz, 1H, ArH), 7.13–7.22 (m, 1H, ArH), 7.29–7.38 (m, 1H, ArH), 8.17 (s, 1H, ArH), 8.50–8.52 (d, $J = 6$ Hz, 1H, ArH), 9.03 (s, 1H, ArH), 11.48 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.4 (CH_3), 24.2 (CH_3), 33.2 (CH_2), 45.4 (CH_2), 56.8 (CH_3), 64.9 (CH), 105.1, 116.2, 117.9, 119.3, 121.6, 121.9, 126.5, 137.3, 140.9, 145.8, 157.2, 159.8, 160.7 (13C_{ar}), 163.1 (C=O), 172.4 (C=O), 180.6 (C=O). Analysis for $C_{22}H_{21}ClN_4O_4S$ (472.94) Calculated: C: 55.87%, H: 4.48%, N: 11.85%; Found: C: 55.91%, H: 4.50%, N: 11.83%.

N-[2-(2-bromo-5-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (24). Yield: 63%; m.p.: 111–113°C. Time of reaction: 16h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.17–1.21 (t, J = 6 Hz, 3H, CH_3), 2.61 (s, 3H, CH_3), 3.37 (s, 2H, CH_2), 4.37–4.43 (q, $J = 6$ Hz, 2H, CH_2), 5.83 (s, 1H, CH), 6.85–6.87 (m, 2H, ArH), 7.10–7.12 (d, $J = 6$ Hz, 1H, ArH), 7.48–7.51 (d, J = 6 Hz, 1H, ArH), 8.18–8.20 (d, $J = 6$ Hz, 1H, ArH), 8.34 (s, 1H, ArH), 11.94 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.4 (CH_3), 24.2 (CH_3), 33.3 (CH_2), 45.7 (CH_2), 66.3 (CH), 105.0, 113.6, 118.4, 119.3, 119.8, 121.9, 135.0, 137.3, 142.8, 145.8, 159.1, 160.4, 160.7 (13C_{ar}), 163.8 (C=O), 172.9 (C=O), 180.1 (C=O). Analysis for $C_{21}H_{18}BrFN_4O_3S$ (505.36) Calculated: C: 49.91%, H: 3.59%, N: 11.09%; Found: C: 49.95%, H: 3.60%, N: 11.06%.

N-[2-(2-chloro-6-fluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (25). Yield: 71%; m.p.: 206–208°C. Time of reaction: 24h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.40–1.44 (t, 3H, CH_3, $J = 6$ Hz), 2.68 (s, 3H, CH_3), 3.52 (s, 2H, CH_2), 4.56–4.64 (q, 2H, CH_2, $J = 6$ Hz), 6.51 (s, 1H, CH), 7.33–7.43 (m, 1H, ArH), 7.46–7.57 (m, 1H, ArH), 8.50–8.52 (d, 1H, ArH, J = 6 Hz), 8.56–8.62 (m, 1H, ArH), 9,03 (s, 1H, ArH). 9.13 (s, 1H, ArH), 11.53 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.7 (CH_3), 24.7 (CH_3), 33.2 (CH_2), 45.6 (CH_2), 61.5 (CH), 105.2, 116.9, 119.3, 121.8, 126.9, 127.5, 130.7, 134.2, 137.3, 145.8, 159.6, 160.1, 160.7 (13C_{ar}), 163.7 (C=O), 172.1 (C=O), 180.2 (C=O). Analysis for $C_{21}H_{18}ClFN_4O_3S$ (460.91) Calculated: C: 54.72%, H: 3.94%, N: 12.16%; Found: C: 54.76%, H: 3.96%, N: 12.13%.

N-[2-(2,3-difluorophenyl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (26). Yield: 76%; m.p.: 179–181°C. Time of reaction: 24h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.35–1.40 (t, J = 9 Hz, $J = 6$ Hz, 3H, CH_3), 2.68 (s, 3H, CH_3), 3.86 (s, 2H, CH_2), 4.54–4.61 (q, $J = 6$ Hz, $J = 9$ Hz, 2H, CH_2), 6.24 (s, 1H, CH), 7.24–7.31 (m, 1H, ArH), 7.41–7.56 (m, 2H, ArH), 8.49–8.52 (d, $J = 9$ Hz, 1H, ArH), 8.59–8.61 (m, 1H, ArH), 9.01 (s, 1H, ArH), 11.43 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.6 (CH_3), 24.2 (CH_3), 33.2 (CH_2), 45.6 (CH_2), 65.0 (CH), 105.0, 118.6, 119.3, 121.9, 122.9, 124.4, 128.9, 137.3, 145.8, 148.4, 152.5, 159.6, 160.8 (13C_{ar}), 163.8 (C=O), 172.3 (C=O), 180.6 (C=O). Analysis for $C_{21}H_{18}F_2N_4O_3S$ (444.45) Calculated: C: 56.75%, H: 4.08%, N: 12.61%; Found: C: 56.78%, H: 4.06%, N: 12.65%.

N-[2-(1H-pyrrol-2-yl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (27). Yield: 62%; m.p.: 228–230°C. Time of reaction: 16h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.17–1.21 (t, $J = 6$ Hz, 3H, CH_3), 2.52 (s, 3H, CH_3), 3.35 (s, 2H, CH_2), 3.96–4.02 (q, J = 6 Hz, 2H, CH_2,), 5.98 (s, 1H, CH), 6.08–6.10 (m, 2H, ArH), 6.86–6.89 (m, 1H, ArH), 7.01–7.03 (d, $J = 6$ Hz, 1H, ArH), 8.03–8.05 (d, $J = 6$ Hz, 1H, ArH), 8.30 (s, 1H, ArH), 11.24 (s, 1H, NH), 14.14 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.4 (CH_3), 14.2 (CH_3), 31.9 (CH_2), 45.5 (CH_2), 64.9 (CH), 105.3, 107.8, 112.1, 119.3, 119.9, 121.9, 137.3, 139.0, 145.8, 159.1, 160.5 (13C_{ar}), 163.4 (C=O), 174.4 (C=O), 180.3 (C=O). Analysis for $C_{19}H_{19}N_5O_3S$ (397.45) Calculated: C: 57.42%, H: 4.82%, N: 17.62%; Found: C: 57.46%, H: 4.85%, N: 17.59%.

N-[2-(5-chlorofuran-2-yl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (28). Yield: 78%; m.p.: 189–191°C. Time of reaction: 16h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.38–1.43 (t, J = 6 Hz, $J = 9$ Hz, 3H, CH_3), 2.69 (s, 3H, CH_3), 3.57 (s, 2H, CH_2), 4.58–4.64 (q, $J = 6$ Hz, 2H, CH_2), 5.51 (s, 1H, CH), 6.46–6.50 (m, 1H, ArH), 6.60–6.68 (m, 1H, ArH), 7.49–7.54 (m, 1H, ArH), 8.55–8.61 (m, 1H, ArH), 9.05 (s, 1H, ArH), 11.84 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.2 (CH_3), 24.2 (CH_3), 31.9 (CH_2), 45.7 (CH_2), 62.1 (CH), 104.9, 108.6, 117.7, 119.3, 121.9, 137.3, 145.8, 158.9, 160.2, 160.7 (13C_{ar}), 163.2 (C=O), 174.5 (C=O), 180.9 (C=O). Analysis for $C_{19}H_{17}ClN_4O_4S$ (432.88) Calculated: C: 52.72%, H: 3.96%, N: 12.94%; Found: C: 52.76%, H: 3.97%, N: 12.92%.

N-[2-(1H-indol-3-yl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (29). Yield: 75%; m.p.: 197–199°C. Time of reaction: 20h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.41–1.45 (t, $J = 6$ Hz, 3H, CH_3), 2.70 (s, 3H, CH_3), 3.66 (s, 2H, CH_2), 4.60–4.68 (q, $J = 9$ Hz, 2H, CH_2), 5.63 (s, 1H, CH), 6.92–7.17 (m, 1H, ArH), 7.33–7.55 (m, 1H, ArH), 7.63–7.71 (m, 1H, ArH), 7.82–7.83 (d, $J = 3$ Hz, 1H, ArH), 8.26–8.29 (d, $J = 9$ Hz, 1H, ArH), 8.55 (s, 1H, ArH), 8.60–8.63 (d, $J = 9$ Hz, 1H, ArH), 9.09 (s, 1H, ArH), 11.58 (s, 1H, NH), 12.85 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.5 (CH_3), 24.4 (CH_3), 31.9 (CH_2), 45.7 (CH_2), 60.9 (CH), 103.8, 105.0, 112.4, 119.3, 119.6, 119.7, 121.9, 123.2, 127.4, 136.5, 137.3, 145.8, 159.0, 160.7 (14C_{ar}), 163.8 (C=O), 174.4 (C=O), 180.4 (C=O). Analysis for $C_{23}H_{21}N_5O_3S$ (447.51) Calculated: C: 61.73%, H: 4.73%, N: 15.65%; Found: C: 61.78%, H: 4.75%, N: 15.62%.

N-[2-(6-chloro-benzo[1,3]dioxol-5-yl)-4-oxo-1,3-thiazolidin-3-yl]-1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxamide (30). Yield: 69%; m.p.: 168–170°C. Time of reaction: 24h. ^{1}H NMR (DMSO-d_6) δ (ppm) = 1.17–1.21 (t, J = 6 Hz, 3H, CH_3), 2.58 (s, 3H, CH_3), 3.42 (s, 2H, CH_2), 4.59–4.65 (q, $J = 6$ Hz, 2H, CH_2,), 4.85 (s, 2H, CH_2), 5.97 (s, 1H, CH), 6.78 (s, 1H, ArH), 6.84 (s, 1H, ArH), 7.11–7.13 (d, J = 6 Hz, 1H, ArH), 7.90 (s, 1H, ArH), 8.17–8.19 (d, $J = 6$ Hz, 1H, ArH), 11.31 (s, 1H, NH); ^{13}C NMR (DMSO) δ (ppm) = 12.4 (CH_3), 24.4 (CH_3), 33.5 (CH_2), 45.8 (CH_2), 65.1 (CH), 102.1,

105.1, 111.1, 119.4, 120.8, 121.9, 132.9, 137.3, 145.8, 146.8, 149.8, 159.7, 160.8 ($13C_{ar}$), 160.7 (C=O), 163.4 (C=O), 172.4 (C=O). Analysis for $C_{22}H_{19}ClN_4O_5S$ (486.93) Calculated: C: 54.27%, H: 3.93%, N: 11.51%; Found: C: 54.32%, H: 3.96%, N: 11.53%.

Microbiology

In vitro *antimicrobial assay*

The examined compounds **17–30** were screened *in vitro* for antibacterial and antifungal activities. Detailed information concerning procedure of antimicrobial assay is presented in the Supplemental Materials.

Conclusions

In conclusion, in this paper we design, synthesized, identified, and evaluated for *in vitro* antimicrobial activity 14 new nalidixic acid–1,3-thiazolidin-4-one hybrids (**17–30**). Our results indicated that newly synthesized compounds **17–30** showed good to moderate antimicrobial activity, especially against Gram-positive bacteria. Moreover, compound **29** inhibited growth of reference strains of Gram-negative bacteria belonging to *Enterobacteriaceae* family.

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