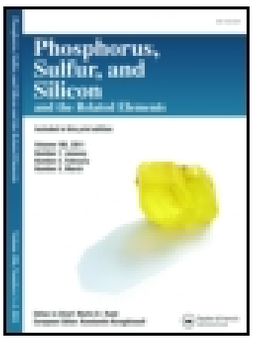

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Synthesis of novel *N*-(naphthalen-1-yl)propanamide derivatives and evaluation their antimicrobial activity

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ABSTRACT

New *N*-(naphthalen-1-yl)propanamide was synthesized and studied for their antimicrobial activity. The final compounds were procured by reacting *N*-(naphthalen-1-yl)propanamide with some 2-mercapto aryl or dithiocarbamate salt derivatives. Their structures were determined by ^{1}H-NMR and ^{13}C-NMR spectroscopy and LC-MS/MS spectral data. The synthesized compounds were investigated for their antimicrobial activities against 10 bacteria and 10 fungi species. All compounds showed notable activity. Especially, compounds 2-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]-*N*-(naphthalen-1-yl)propanamide **(2a)**, 2-(benzothiazol-2-ylthio)-*N*-(naphthalen-1-yl)propenamide **(2b)**, 2-[(1-methyl-1*H*-imidazol-2-yl)thio]-*N*-(naphthalen-1-yl)propanamide **(2c)**, and *N*-(naphthalen-1-yl)-2-[(5-nitro-1*H*-benzimidazol-2-yl)thio]propanamide **(2e)** exhibited antifungal activity against at least one fungus at the half potency of ketoconazole. Also, 2-[(1-methyl-1*H*-imidazol-2-yl)thio]-*N*-(naphthalen-1-yl)propanamide **(2c)**, *N*-(naphthalen-1-yl)-2-[(5-nitro-1*H*-benzimidazol-2-yl)thio]propanamide **(2e)** and 2-[(4-methyl-4*H*-1,2,4-triazol-3-yl)thio]-*N*-(naphthalen-1-yl)propanamide **(2f)** showed anti-gram-positive bacterial activity at the half potency of chloramphenicol. Only one compound, 2-(benzothiazol-2-ylthio)-*N*-(naphthalen-1-yl)propanamide (**2b**) displayed anti-gram-negative bacterial activity against *Yersinia enterocolitica* (Y53).

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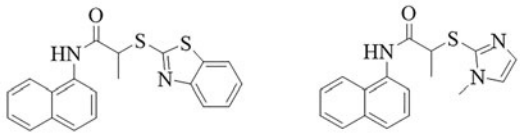
Naphthalene; propanamide; antimicrobial activity

GRAPHICAL ABSTRACT



compound 2b compound 2c

Introduction

In nature, multicellular organisms live harmoniously with microorganisms. If this harmony gets disrupted, an inflammatory response can occur depending on the pathogenic microorganisms present. These inflammatory responses remove harmful stimuli for the purposes of protection. Some pathogenic infections are also related to contagious diseases. These diseases can be transmitted through environmental factors, such as water, food, and air.[1–3] Therefore, researchers focus on preventing the spread of disease, controlling disease transmission, or killing the pathogenic microbes responsible for infection.[4] Recently, one major threat to human health surrounding pathogenic microorganisms is the development of multidrug resistance (MDR), commonly known as drug-resistance (XDR) and pan-drug resistance (PDR).[5]

In recent years, global mortality and morbidity rates have extensively increased due to the emergence of antimicrobial resistance developed by certain bacteria and fungi.[6,7] The World Health Organization (WHO) released a list of 12 bacteria and bacterial families that are often implicated in MDR. One of the most concerning microorganisms in this list is *Staphylococcus aureus*, since this bacterium is known to be potentially life-threatening, particularly by causing acquired infections in hospitals. Outside of medical centers, these pathogenic microorganisms also pose risks not only to patients, but also to healthy individuals in society.[8,9] Likewise, Candida species, especially *Candida albicans* have been reported to develop resistance to chemotherapeutic agents, as presented in several reports.[10–13] To combat these health risks, one area of focus is the synthesis of new antimicrobial agents to increase therapeutic alternatives in cases of MDR.[14,15]

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According to the literature, the naphthalene ring system has been demonstrated to harbor various therapeutic properties, such as antimycobacterial,[16] antibacterial,[17] antifungal,[18–20] anticonvulsant,[21] anticancer,[22,23] tyrosine kinase inhibition,[24] DNA protective functions,[25] inhibition of tyrosyl-tRNA synthetase,[26] anti-inflammatory,[27,28] herbicidal,[29] and anti-HIV [30] activities. In particular, various N-(naphthalen-1/2-yl)amide derivatives show remarkable antimicrobial activity.[31–34] Tolnaftate and naftifine are two examples of antimicrobial agents in this group that contain the naphthalene ring as shown in Figure S1.[35–38]

In addition to compounds containing the naphthalene ring, (benz)azole derivatives like imidazole, triazole, thiadiazole benzimidazole, and benzothiazole have been reported to exhibit strong antibacterial and antifungal activities.[39–44] Furthermore, (benz)azole derivatives containing a naphthalene group have also been tested for their antimicrobial activity.[45–48] Specifically, *N*-methylimidazole derivatives have been of particular interest because they have been shown to exhibit strong antibacterial activity specifically against *S. aureus* and drug-resistant *S. aureus*.[49,50]

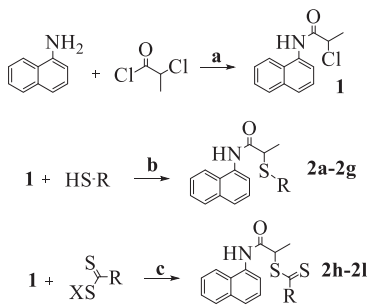
Based on these preliminary findings, this research was directed towards the synthesis and development of novel *N*-(naphthalen-1-yl)propanamide derivatives and investigation of their antifungal and antibacterial activities.

Results and discussion

Chemistry

In this work, we synthesized 11 compounds that included *N*-(naphthalen-1-yl)propanamide in the core structure. The synthesis reaction was carried out via two steps. In the first step, naphthalen-1-amine was acylated with 2-chloropropionyl chloride. Then the obtained product (**1**) was reacted with 2-mercapto aryl derivatives to gain the final compounds **2a–2g**. And compound (**1**) was also reacted with dithiocarbamate salt derivatives to obtain final compounds **2h–2k** as shown in Scheme 1. All the synthesized compounds were fully characterized by their analytical and spectral data.

The ^{1}H-NMR spectra of synthesized compounds (**2a–2k**) showed doublet or multiplet signals at δ 1.55–1.81 ppm for methyl (CH_3) proton of propanamide. The quartets or multiplet peaks seen at δ 4.41–5.18 ppm for methylene (CH) proton of propanamide. The broad single peak seen at δ 10.09–11.09 ppm indicated the N-H proton of propanamide. The appearance of singlets, doublets, triplets, and/or multiplet peaks at δ 6.71–8.68 ppm was due to the aromatic protons. The ^{13}C-NMR spectra of compounds showed signals at δ 110.10–168.27 ppm for aromatic carbon. Carbonyl (C = O) carbon was seen at δ 170.18–171.15 ppm and thiocarbonyl (C = S) carbon was seen at δ 190.81–194.68 ppm. M + 1 peaks in LC-MS/MS spectra were compatible with the calculated molecular weight of the target compounds (**2a–2k**).



Scheme 1. The synthesis diagram of the compounds. *Reactions & conditions:* (**a**) TEA, THF, $ClCOCH_2Cl$, 0–5 °C, then r.t 3 h; (**b**) Acetone, Potassium carbonate, rt; (**c**) Acetone, rt.

Prediction of ADME parameters

ADME (Absorption, Distribution, Metabolism, and Excretion) properties of the synthesized compounds (**2a–2k**) and reference drugs (chloramphenicol and ketoconazole) were calculated using Molinspiration software and Molsoft software.[51,52] The Log P values were found between 2.70 and 5.42 for the synthesized compounds. For all molecules, number of hydrogen bond donor (HBD) was stated as 1, except compounds **2d** and **2e**. Also, hydrogen bond acceptor (HBA) for all compounds was determined between 2 and 5. The number of stereo centers was stated as 1 for the synthesized compounds. The results are in the congruent range according to Lipinski's rule of 5. Even if there is no exact finding in practice, these scores are in harmony with the activity potential of the compounds. Drug-likeness model scores (DLMS) were found between −0.65 and 1.47. All findings were shown in Table S1 (Supplemental Materials). According to these results, all compounds have a good pharmacokinetic profile. These findings predict that these synthesized compounds may be considered as oral antimicrobial agents.

Antimicrobial activity

The antimicrobial activity of the compounds **2a–2k** was determined by finding MIC values shown in Table S2 (Supplemental Materials). And their antimicrobial activity was evaluated versus the standard drugs, chloramphenicol and ketoconazole.

All compounds exhibited antifungal activity. Particularly, compounds **2a**, **2b**, and **2e** (MIC: 187.5 µg/ml) were found more effective than the synthesized compounds against *C. albicans* (ATCC 90028), and their anticandidal activity was determined as half the potency of ketoconazole (MIC: 93.75 µg/ml). Also, compound **2c** displayed notable anticandidal activity against *Candida krusei* (ATCC 6258) at half the potency of ketoconazole. Compounds **2a**, **2b**, **2g**, **2h**, and **2i** exhibited anticandidal activity at same concentration (MIC: 187.5 µg/ml) against *Candida glabrata* (ATCC 90030). Except compound **2e**, all compounds showed antifungal activity at the quarter potency of ketoconazole against *Fusarium solani* (obtained from our laboratory). Compounds **2a**, **2c**, **2d**, **2f**, **2g**, **2i**, **2j**, and **2k** displayed antifungal activity against *Fusarium moniliforme* (NRRL 2374) at the quarter potency of ketoconazole.

Compounds **2a**, **2c**, and **2i** (MIC: 375 µg/ml) were stated more effective than the other synthesized compounds against *Penicillium chrysogenum* (ATCC 10106). Compounds

2a, **2b**, **2c**, **2d**, **2i**, and **2j** (MIC: 375 µg/ml) were found more active than the other compounds against *Penicillium citrinum* (ATCC 9849). All compounds (**2a–2k**) exhibited antifungal activity at the same concentration (MIC: 375 µg/ml) against *Penicillium expansum* (ATCC 24692). Compounds **2a–2i** displayed anticandidal activity at the same concentration (MIC: 375 µg/ml) against *Candida parapsilosis* (ATCC 22019). Compounds **2a**, **2b**, and **2c** (MIC: 375 µg/ml) were stated more active than the other compounds against *Aspergillus niger* (ATCC 9807). But the activity results described in this paragraph, unfortunately, are not meaningful enough to explain the activity-structure relationship.

According to the antifungal activity results, the sulfur bridged derivatives (**2a–2g**) were more active than dithiocarbamate bridged derivatives (**2h–2k**). The synthesized compounds showed slightly better activity against *C. albicans* (ATCC 90028) than the other fungi. Especially, 2-methylthiadiazol-2-yl (**2a**) and *N*-methyl-imidazol-2-yl (**2c**) substitutions at the second position on propanamide increased the activity. Their log P values, molecular weights and molecular volumes correlate with the properties of ketoconazole. However, benzothiazole-2-yl (**2b**) and *N*-(naphthalen-1-yl)-2-[(5-nitro-1*H*-benzimidazol-2-yl)thio]propanamide (**2e**) substitutions at same position may also increase antifungal activity. Also, the findings proved that the electron withdrawing group (**2c**) has positively increased antibacterial activity in comparison with electron donating group (**2d**).

All compounds showed antibacterial activity. Especially, compounds **2c**, **2e**, and **2f** displayed antibacterial activity against *S. aureus* (ATCC 6538) at half potency of chloramphenicol (MIC: 93.75 µg/ml). Also, compound **2b** (MIC: 187.5 µg/ml) was determined as the most active compound against *Yersinia enterocolitica* (Y53), but no more than chloramphenicol (MIC: 93.75 µg/ml). Additionally, compound **2c** demonstrated good anti-gram-positive bacterial activity in comparison with the other synthesized compounds against *Bacillus cereus* (ATCC 10876) and *Bacillus subtilis* (NRRL NRS-744). But, all compounds presented the lowest activity against *Enterococcus faecalis* (ATCC 51299), *Klebsiella pneumoniae* (ATCC 700603), and *Micrococcus luteus* (NRRL B-4375). On the other hand, compounds **2a**, **2b**, **2e**, **2g**, **2h**, and **2j** displayed the lower activity than chloramphenicol against *Listeria monocytogenes* (ATCC 19111). Also, compounds **2c** and **2e** increased the antibacterial activity against *Escherichia coli* (ATCC 25922).

In the antibacterial activity investigation, the sulfur bridged derivatives (**2a–2g**) were more active than dithiocarbamate bridged derivatives (**2h–2k**). In particularly, *N*-methyl-imidazol-2-yl (**2c**) substitution exhibited positively effect on antibacterial activity. In general, the activity against gram-positive bacteria was found greater than the activity against gram-negative bacteria.

Experimental

Chemistry

All chemicals were purchased from Sigma-Aldrich Chemical Co (Sigma-Aldrich Corp., St. Louis, MO, USA) and Merck Chemicals (Merck KGaA, Darmstadt, Germany). All melting points (m.p.) were determined by MP90 digital melting point apparatus (Mettler Toledo, Ohio, USA) and were uncorrected. All reactions were monitored by thin-layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). Spectroscopic data were recorded with the following instruments: IR Shimadzu 8400S spectrophotometer (Shimadzu, Tokyo, Japan), ^{1}H NMR (nuclear magnetic resonance) Bruker DPX 300 FT-NMR spectrometer, ^{13}C NMR, Bruker DPX 75 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA) M + 1 peaks were determined by Shimadzu 8040 LC/MS/MS system (Shimadzu, Tokyo, Japan).

Materials and methods

General procedure for the synthesis of 2-chloro-N-(naphthalen-1-yl)propanamide derivatives (1)

Naphthalen-1-amine (0.05 mol, 7.16 g) and triethylamine (0.05 mol, 8.47 mL) were dissolved in THF (150 mL) with a constant stirring at 0–5 °C, then 2-chloropropyl chloride (0.05 mol, 5.82 mL) was added dropwise gradually to this solution. The reaction mixture thus obtained was further stirred for 2 h at 0–5 °C. The reaction was monitored by TLC. After the solvent was vaporized to dryness, the solid was filtered and washed with water. Finally, the raw product was recrystallized from ethanol.

2-(Substituted thio)-N-(naphthalen-1-yl)propanamide derivatives (2a–2g)

A mixture of *N*-(naphthalen-1-yl)propanamide (1.50 mmol, 0.35 g) and mercapto derivatives (1.50 mmol) were dissolved in acetone (15 ml). For catalytic purposes, potassium carbonate (1.50 mmol, 0.21 g) was added to the round bottom flask. After 2 h, the reaction was monitored by TLC. Ultimately the solvent was vanished to dryness, the solid was filtered and washed with water. The final products were recrystallized from ethanol.

1-(Naphthalen-1-ylamino)-1-oxopropan-2-yl substituted-1-carbodithioate derivatives (2h–2k)

A mixture of *N*-(naphthalen-1-yl)propanamide (1.50 mmol, 0.35 g) and dithiocarbamate derivatives (1.50 mmol) were dissolved in acetone (15 mL). After 4 h, the reaction was monitored by TLC. Ultimately the solvent was vanished to dryness, the solid was filtered and washed with water. The final products were recrystallized from ethanol.

2-[(5-Methyl-1,3,4-thiadiazol-2-yl)thio]-N-(naphthalen-1-yl)propanamide (2a)

m. p. 63–66 °C, yield 73%, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.73 (d, J = 6.96 Hz, 3H, CH_3), 2.71 (s, 3H, thiadiazole-CH_3), 4.90–4.97 (q, J_1 = 6.88 Hz, J_2 = 14.62 Hz, H, CH), 7.48–7.58 (m, 3H, Ar-H), 7.70 (d, J = 7.17 Hz, H, Ar-H), 7.79 (d, J = 8.1 Hz, H, Ar-H), 7.93–7.96 (m, H, Ar-H), 8.08 (d, J = 7.74 Hz, H, Ar-H), 10.41 (brs, H, NH). ^{13}C-

NMR (75 MHz, DMSO-d_6, ppm) 15.73 (CH_3), 19.18 (CH_3), 47.63 (CH), 122.30, 123.03, 126.01, 126.21, 126.49, 126.60, 133.38, 134.16, 163.31, 167.07, 170.18 (C = O). For $C_{16}H_{15}N_3OS_2$ calculated: HRMS (*m/z*): $[M+1]^+$ calculated 330.0729; found 330.0724.

2-(Benzothiazol-2-ylthio)-N-(naphthalen-1-yl)propanamide (2b)

m. p. 126–128 °C, yield 70%, IR (KBr) V_{max} (cm^{-1}): 3334 (N-H), 1674 (C = O), 1541–1427 (C = C and C = N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.81 (d, J = 6.99 Hz, 3*H*, CH_3), 5.11–5.18 (m, H, CH), 7.41 (t, J = 7.58 Hz, H, Ar-H), 7.49–7.53 (m, 4H, Ar-H), 7.71 (d, J = 7.38 Hz, H, Ar-H), 7.80 (d, J = 8.1 Hz, H, Ar-H), 7.96 (d, J = 7.56 Hz, 2H, Ar-H), 8.06 (d, J = 7.95 Hz, H, Ar-H), 8.12 (d, J = 7.41 Hz, H, Ar-H), 10.47 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 19.33 (CH_3), 47.41 (CH), 121.65, 122.33, 122.43, 123.02, 125.23, 126.02, 126.21, 126.44, 126.58, 128.31, 128.63, 133.43, 134.15, 135.36, 153.08, 165.61, 170.27 (C = O). For $C_{20}H_{16}N_2OS_2$ calculated: HRMS (*m/z*): $[M+1]^+$ calculated 365.0777; found 365.0777.

2-[(1-Methyl-1H-imidazol-2-yl)thio]-N-(naphthalen-1-yl)propanamide (2c)

m. p. 68–72 °C, yield 82%, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.55 (d, J = 6.96 Hz, 3H, CH_3), 3.68 (s, 3H, imidazole-CH_3), 4.51–4.58 (q, J_1 = 6.74 Hz, J_2 = 13.71 Hz, H, CH), 7.25 (s, H, Ar-H), 7.46–7.56 (m, 4H, Ar-H), 7.71–7.78 (m, 2H, Ar-H), 7.92–7.95 (m, H, Ar-H), 8.05 (d, J = 7.05 Hz, H, Ar-H), 10.58 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 18.44 (CH_3), 34.17 (CH_3), 46.90 (CH), 121.73, 123.07, 124.94, 125.87, 126.01, 126.40, 126.54, 127.84, 128.01, 128.59, 133.63, 134.15, 138.73, 170.85 (C = O). For $C_{17}H_{17}N_3OS$ calculated: HRMS (*m/z*): $[M+1]^+$ calculated 312.1165; found 312.1165.

2-[(5-Methoxy-1H-benzimidazol-2-yl)thio]-N-(naphthalen-1-yl)propanamide (2d)

m. p. 124–126 °C, yield 85%, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.70–1.73 (m, 3H, CH_3), 3.74 and 3.79 (2 s, 3H, O-CH_3), 4.94–5.02 (m, H, CH), 6.71–6.75 (m, H, Ar-H), 6.83–6.87 (m, H, Ar-H), 7.05–7.08 (m, H, Ar-H), 7.49–7.60 (m, 3H, Ar-H), 7.67–7.96 (m, 3H, Ar-H), 8.07–8.18 (m, H, Ar-H), 10.73 (brs, H, NH), 12.42 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 18.68 (CH_3), 45.25 (CH), 55.07 (OCH_3), 110.17, 110.45, 111.61, 121.08, 122.60, 122.80, 123.01, 125.63, 126.53, 128.65, 133.57, 133.72, 134.12, 148.64, 156.14, 168.27, 170.90 (C = O). For $C_{21}H_{19}N_3O_2S$ calculated: HRMS (*m/z*): $[M+1]^+$ calculated 378.1271; found 378.1274.

N-(naphthalen-1-yl)-2-[(5-nitro-1H-benzimidazol-2-yl)thio]-propanamide (2e)

m. p. 88–90 °C, yield 80%, IR (KBr) V_{max} (cm^{-1}): 3205 (N-H), 1670 (C = O), 1558–1404 (C = C and C = N), 1550–1340 (NO_2). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.72 (d, J = 7.07 Hz, 3H, CH_3), 5.02–5.09 (q, J_1 = 7.05 Hz, J_2 = 14.16 Hz, H, CH), 7.49–7.74 (m, 5H, Ar-H), 7.91 (d, J = 7.80 Hz, 2H, Ar-H), 8.00–8.04 (dd, J_1 = 2.17 Hz, J_2 = 8.85 Hz, H, Ar-H), 8.25–8.27 (m, H, Ar-H), 8.37 (s, H, Ar-H), 11.09 (brs, H, NH), 12.45 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 18.53 (CH_3), 44.62 (CH), 110.79, 113.94, 117.06, 120.60, 122.78, 125.38, 126.13, 126.31, 126.52, 127.47, 128.67, 133.92, 134.12, 141.58, 141.99, 147.12, 159.18, 171.15 (C = O). For $C_{20}H_{16}N_4O_3S$ calculated: HRMS (*m/z*): $[M+1]^+$ calculated 393.1016; found 393.1020.

2-[(4-Methyl-4H-1,2,4-triazol-3-yl)thio]-N-(naphthalen-1-yl)propanamide (2f)

m. p. 93–96 °C, yield 76%, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.64 (d, J = 6.78 Hz, 3H, CH_3), 3.62 (s, 3H, triazole-CH_3), 4.64 (q, J_1 = 6.62 Hz, J_2 = 13.46 Hz, H, CH), 7.53–7.56 (m, 3H, Ar-H), 7.71 (d, J = 7.2 Hz, H, Ar-H), 7.78 (d, J = 8.31, H, CH_3), 7.92–7.95 (m, H, Ar-H), 8.03–8.11 (m, H, Ar-H), 8.68 (s, H, Ar-H), 10.38 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 18.95 (CH_3), 31.56 (triazole-CH_3), 46.71 (CH_3), 122.07, 123.03, 126.01, 126.09, 126.46, 126.58, 128.61, 133.46, 134.15, 143.11, 147.02, 148.22, 170.62 (C = O). For $C_{16}H_{16}N_4OS$ calculated: HRMS (*m/z*): $[M+1]^+$ calculated 313.1118; found 313.1120.

N-(naphthalen-1-yl)-2-(phenyl thio)propanamide (2g)

m. p. 91–93 °C, yield 73%, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.55 (d, J = 6.93 Hz, 3H, CH_3), 4.41 (q, J_1 = 6.88 Hz, J_2 = 14.12 Hz, H, CH), 7.32–7.42 (m, 3H, Ar-H), 7.49–7.62 (m, 6H, Ar-H), 7.78 (d, J = 8.13 Hz, H, Ar-H), 7.84–7.86 (m, H, Ar-H), 7.91–7.94 (m, H, Ar-H), 10.10 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 18.35 (CH_3), 46.25 (CH), 122.42, 123.06, 125.99, 126.04, 126.32, 126.52, 127.92, 128.56, 129.57, 132.23, 133.58, 134.14, 171.25 (C = O). For $C_{19}H_{17}NOS$ calculated: HRMS (*m/z*): $[M+1]^+$ calculated 308.1104; found 308.1102.

1-(Naphthalen-1-ylamino)-1-oxopropan-2-yl piperidine-1-carbodithioate (2h)

m. p. 102–104 °C, yield 75%, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.61 (brs, 6H, piperidine-CH_2), 1.70 (d, J = 7.11 Hz, 3H, CH_3), 3.91 (s, 2H, piperidine-CH_2), 4.23 (s, 2H, piperidine-CH_2), 5.00 (q, J = 7.15 Hz, H, CH), 7.48–7.57 (m, 3H, Ar-H), 7.7 (d, J = 7.29 Hz, H, Ar-H), 7.79 (d, J = 8.13 Hz, H, Ar-H), 7.93–7.96 (m, H, Ar-H), 8.14 (d, J = 8.19 Hz, H, Ar-H), 10.25 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 18.75 (CH_3), 23.96 (piperidine-CH_2), 25.71 (piperidine-CH_2), 26.32 (piperidine-CH_2), 50.92 (CH), 51.68 (piperidine-CH_2), 52.64 (piperidine-CH_2), 122.28, 123.16, 126.01, 126.37, 126.53, 128.40, 128.61, 133.73, 134.18, 170.81 (C = O), 190.81 (C = S). For $C_{19}H_{22}N_2OS_2$ calculated: HRMS (*m/z*): $[M+Na]^+$ calculated 381.1066; found 381.1075.

1-(Naphthalen-1-ylamino)-1-oxopropan-2-yl morpholine-4-carbodithioate (2i)

m. p. 185–188 °C, yield 79%, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.68–1.71 (m, 3H, CH_3), 3.69 (t, $J = 4.43$ Hz, 4H, morpholine-CH_2), 3.98 (s, 2H, piperidine-CH_2), 4.23 (s, 2H, morpholine-CH_2), 4.95–5.05 (m, H, CH), 7.47–7.57 (m, 3H, Ar-H), 7.62–7.64 (m, H, Ar-H), 7.79 (d, $J = 8.30$ Hz, H, Ar-H), 7.93–7.96 (m, H, Ar-H), 8.04–8.11 (m, H Ar-H), 10.29 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 18.56 (CH_3), 50.89 (CH), 55.05 (morpholine N-CH_2), 66.07 (morpholine O-CH_2), 122.42, 123.20, 126.00, 126.09, 126.40, 126.54, 128.58, 133.67, 134.16, 170.64 (C = O), 194.68 (C = S). For $C_{18}H_{20}N_2O_2S_2$ calculated: HRMS (m/z): $[M + Na]^+$ calculated 383.0858; found 383.0862.

1-(Naphthalen-1-ylamino)-1-oxopropan-2-yl 4-(pyrimidin-2-yl)piperazine-1-carbodithioate (2j)

m. p. 170–172 °C, yield 80%, IR (KBr) V_{max} (cm^{-1}): 3250 (N-H), 1660 (C = O), 1589–1417 (C = C and C = N). ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.71 (d, $J = 7.17$ Hz, 3H, CH_3), 3.90 (s, 4H, piperazine-CH_2), 4.09 (s, 2H, piperidine-CH_2), 4.36 (s, 2H, piperazine-CH_2), 4.94–5.04 (m, H, CH), 7.69 (t, $J = 4.67$ Hz, H, Ar-H), 7.47–7.59 (m, 3H, Ar-H), 7.65 (d, $J = 7.24$ Hz, H, Ar-H), 7.79 (d, $J = 8.39$ Hz, H, Ar-H), 7.93–7.96 (m, H, Ar-H), 8.09–8.12 (m, H, Ar-H), 8.41 (d, $J = 4.75$ Hz, 2H, Ar-H), 10.28 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 18.86 (CH_3), 42.98 (CH), 50.99 (CH_2), 55.06 (CH_2), 111.10, 122.42, 123.20, 126.01, 126.09, 126.41, 126.55, 128.59, 133.68, 134.16, 158.47, 161.29, 170.67 (C = O), 194.44 (C = S). For $C_{22}H_{23}N_5OS_2$ calculated: HRMS (m/z): $[M + 1]^+$ calculated 438.1417; found 438.1413.

1-(Naphthalen-1-ylamino)-1-oxopropan-2-yl 4-phenylpiperazine-1-carbodithioate (2k)

m. p. 116–118 °C, yield 75%, ^{1}H-NMR (300 MHz, DMSO-d_6, ppm) δ 1.70 (d, $J = 7.12$, 3H, CH_3), 2.45 (brs, 4 H, piperazine-CH_2), 3.93 (s, 2H, piperidine-CH_2), 4.26 (s, 2H, piperidine-CH_2), 4.97–5.04 (m, H, CH), 7.25–7.34 (m, 5H, Ar-H), 7.47–7.56 (m, 3H, Ar-H), 7.68 (d, $J = 7.03$ Hz, H, Ar-H), 7.77 (d, $J = 8.28$ Hz, H, Ar-H), 7.92–7.95 (m, H, Ar-H), 8.11–8.14 (m, H, Ar-H), 10.28 (brs, H, NH). ^{13}C-NMR (75 MHz, DMSO-d_6, ppm) 18.82 (CH_3), 51.01 (CH_2), 52.41 (CH), 55.08 (CH_2), 122.33, 123.19, 126.02, 126.40, 126.54, 127.61, 128.73, 129.43, 133.72, 134.19, 137.95, 170.71 (C = O), 194.11 (C = S). For $C_{24}H_{25}N_3OS_2$ calculated: HRMS (m/z): $[M + 1]^+$ calculated 436.1512; found 436.1515.

Antimicrobial study

Mueller-Hinton agar plates were used to maintain bacterial cultures. Potato dextrose (PD) agar and Sabouraud dextrose (SD) agar were used for the maintenance of fungal cultures. Test bacteria were acquired from bacterial cultures the incubation of which was performed for 24 h at 37 °C on Mueller-Hinton agar substrate and the dilution of which was performed in accordance with the 0.5 McFarland standard to about 108 CFU/mL. Fresh mature cultures at the age of 3 to 7 d growing at 30 °C on a PD agar substrate were used for the preparation of fungal spore suspensions. Sterile 0.1% Tween 80 was used for the rinsing of the spores and their further dilution to about 10^6 CFU/mL was performed in accordance with the procedural recommendations of CLSI.[53]

Minimum inhibitory concentration (MIC) of the substances was determined by a serial dilution technique using 96-well microtiter plates. A stock solution of 60 mg of each of the substances in 6 mL DMSO (20%) was prepared, and subsequently diluted ten times with twofold serial dilution method. Mueller-Hinton broth was utilized in the case of bacterial cultures and SD broth was utilized in the case of fungal cultures. A number of dilutions, the concentrations of which varied between 6.0 mg/ml and 11.71 μg/mL from bacterium, yeasts and fungal spore solutions and dilutions were transferred into microtitration plates and incubated for 24–48 h at 35–37 °C for bacteria/yeasts and 25 °C for filamentous fungi. One of the positive controls contained 100 μL of microorganism solution plus 20% DMSO solution in a well and another one had 100 μL of microorganism solution plus 100 μL Mueller-Hinton broth in a well. A third control was chloramphenicol for bacterium and ketoconazole for fungi. Negative controls contained only dilute solutions without microorganism. Positive and negative results were evaluated according to turbidity occurred after 24–48 h by comparing to the ones in the control wells. The lowest concentrations giving no visible growth for each microorganism were defined as MIC. The determination of the minimal inhibitory concentration was performed using resazurin, which indicates oxidation-reduction and is employed for the assessment of microbial growth. Resazurin represents a non-fluorescent dye of blue color which turns pink and fluorescent in the case of reduction to resazurin with oxidoreductases inside viable cells. The minimal inhibitory concentration (MIC) for the microorganism examined at the determined concentration was described as the boundary dilution with no altering color of resazurin.[54]

Antimicrobial activity was investigated for compounds **2a–2k**. Their antimicrobial activities were tested against *B. cereus* (ATCC 10876), *B. subtilis* (NRRL NRS-744), *E.* coli (ATCC 25922), *E. faecalis* (ATCC 51299), *K. pneumoniae* (ATCC 700603), *L. monocytogenes* (ATCC 19111), *M. luteus* (NRRL B-4375), *Salmonella typhimurium* (ATCC 14028), *S. aureus* (ATCC 6538), *Y. enterocolitica* (Y53), *C. albicans* (ATCC 90028), *C. glabrata* (ATCC 90030), *C. krusei* (ATCC 6258), *C. parapsilosis* (ATCC 22019), *P. chrysogenum* (ATCC 10106), *P. citrinum* (ATCC 9849), *P. expansum* (ATCC 24692), *F. solani* (obtained from our laboratory), *F. moniliforme* (NRRL 2374) and *A. niger* (ATCC 9807).

Conclusion

In this work, we synthesized novel 11 *N*-(naphthalen-1-yl)propanamide derivatives and evaluated their antimicrobial activity. Results showed that the 2-substituted-*N*-(naphthalen-1-yl)propanamide moiety provides good antimicrobial activity. Notedly, compounds **2a**, **2b**, and **2c** exhibited

antifungal activity against *C. albicans* (ATCC 90028), *C. krusei* (ATCC 6258), and *A. niger* (ATCC 9807). Also, compounds **2c**, **2e**, and **2f** were the most active compounds against *S. aureus* (ATCC 6538). In summary, considering the inhibition activity shown against both microorganism species, the most active compounds were determined to be **2b** and **2c**.

Disclosure statement

The author confirms that this article content has no conflict of interest.

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