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Original article

Synthesis and Antimicrobial Activity of Benzimidazole-Based Acetamide Derivatives

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In the current work, new benzimidazole-based acetamide derivatives (**2a-u**) were synthesized and screened for their in vitro antimicrobial activity. Among these derivatives, compounds **2b-2g** were found to be the most promising antibacterial agents against Pseudomonas aeruginosa. These compounds and streptomycin exhibited the same level of antibacterial activity with a MIC value of 125 µg/mL. Compounds **2p**, **2s**, **2t** and **2u** were the most potent antifungal derivatives against Candida krusei with a MIC value of 125 µg/mL when compared with ketoconazole (MIC= 62.5 µg/mL). Compounds **2s** and **2u** also exhibited the highest inhibitory activity against Fusarium solani with a MIC value of 125 µg/mL, whereas ketoconazole showed its antifungal activity with a MIC value of 62.5 µg/mL.

Key words: Amide, Antimicrobial activity, Benzimidazole.

Benzimidazol Taşıyan Asetamit Türevlerinin Sentezi ve Antimikrobiyal Etkileri

Bu çalışmada, yeni benzimidazol taşıyan asetamit türevleri **(2a-u)** sentezlendi ve in vitro antimikrobiyal etkileri için tarandı. Bu türevler arasında, **2b-2g** bileşikleri Pseudomonas aeruginosa'ya karşı en ümit verici antibakteriyel maddeler olarak bulundu. Bu bileşikler ve streptomisin 125 µg/mL'lik bir MIC değeri ile aynı düzeyde antibakteriyel etki gösterdiler. Ketokonazol (MIC = 62.5 µg/mL) ile karşılaştırıldığında, **2p, 2s, 2t** ve **2u** bileşikleri 125 µg/mL'lik bir MIC değeri ile Candida krusei'ye karşı en etkili antifungal türevlerdi. **2s** ve **2u** bileşikleri 125 µg/mL'lik bir MIC değeri ile Fusarium solani'ye karşı da en yüksek inhibe edici aktiviteyi gösterirken, ketokonazol antifungal etkisini 62.5 µg/mL'lik bir MIC değeri ile gösterdi.

Anahtar kelimeler: Amit, Antimikrobiyal etki, Benzimidazol.

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INTRODUCTION

Infectious diseases pose a continuous and serious threat to human health and life. Despite the increasing number of currently available antimicrobial agents, the emergence of multidrug-resistant microorganisms remains a major challenge for the treatment of bacterial and fungal infections. Due to the failure of current treatments and deaths in immunocompromised patients, substantial attention has been focused on the mechanisms underlying drug resistance as well as on the development of new antimicrobial agents (1-5).

Imidazoles and their fused heterocyclic derivatives are building blocks for many bioactive compounds that play an important role in medicinal chemistry owing to their significant properties as therapeutics in

clinical applications (6). Benzimidazole, a structural isostere of indole and purine nuclei, can be identified as 'Master Key' since it is an important pharmacophore and a privileged scaffold in medicinal chemistry. Due to its synthetic importance and broad spectrum of biological activities, benzimidazole has become an indispensable anchor for the development of new drugs (7-20).

Medicinal chemists have carried out considerable research on amide derivatives. Penicillins and cephalosporins, which possess cyclic amide as the main scaffold and acetamide moiety as the side chain, are widely used antibiotics for the treatment of systemic infections (21).

On the basis of these findings, herein we reported the synthesis and *in vitro* evaluation of benzimidazole-based acetamide derivatives as new antibacterial and antifungal agents.

EXPERIMENTAL

Chemistry

All chemicals were purchased from commercial suppliers and were used without further purification. Melting points were determined on an Electrothermal 9100 melting point apparatus (Weiss-Gallenkamp, Loughborough, UK) and were uncorrected. ^{1}H-NMR spectra were recorded on a Bruker spectrometer (Bruker, Billerica, USA), whereas mass spectra were recorded on a VG Quattro Mass spectrometer (Agilent, Minnesota, USA). Elemental analyses were performed on a Perkin Elmer EAL 240 elemental analyser (Perkin-Elmer, Norwalk, USA). TLC was performed on Kieselgel 60 F_{254} (Merck) layer using petroleum ether:ethyl acetate (3:1 v/v) as eluents.

General procedure for the synthesis of the compounds

2-Chloro-N-(1-methyl-1H-benzimidazol-2-yl)acetamide (1)

Chloroacetyl chloride (0.1 mol) was added dropwise with stirring to a mixture of 1-methyl-1*H*-benzimidazol-2-amine (0.1 mol) and triethylamine (0.1 mol) in THF (50 mL) at 0-5 °C. The solvent was evaporated under reduced pressure. The residue was washed with water to remove triethylamine hydrochloride and crystallized from ethanol (22).

N-(1-Methyl-1H-benzimidazol-2-yl)-2-(arylthio)acetamide derivatives (2a-j)

A mixture of 2-chloro-*N*-(1-methyl-1*H*-benzimidazol-2-yl)acetamide (**1**) (2 mmol) and aryl thiol (2 mmol) in acetone (10 mL) was stirred at room temperature for 10 hours in the presence of potassium carbonate (2 mmol) and filtered. The residue was washed with water and crystallized from ethanol.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(4-methyl-4H-1,2,4-triazol-3-yl)thio]acetamide (2a)

^{1}H-NMR (400 MHz, DMSO-d_6): 3.59 (s, 3H), 3.76 (s, 3H), 4.24 (s, 2H), 7.20-7.50 (m, 4H), 8.54 (s, 1H), 12.40 (s, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 303.
Anal. Calcd. for $C_{13}H_{14}N_6OS$: C, 51.64; H, 4.67; N, 27.80; Found: C, 51.63; H, 4.65; N, 27.79.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(5-methyl-1,3,4-thiadiazol-2-yl)thio]acetamide (2b)

^{1}H-NMR (400 MHz, DMSO-d_6): 2.64 (s, 3H), 3.59 (s, 3H), 4.07 (s, 2H), 7.20-7.51 (m, 4H), 12.40 (s, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 320.
Anal. Calcd. for $C_{13}H_{13}N_5OS_2$: C, 48.88; H, 4.10; N, 21.93; Found: C, 48.89; H, 4.12; N, 21.91.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(1-methyl-1H-tetrazol-5-yl)thio]acetamide (2c)

^{1}H-NMR (400 MHz, DMSO-d_6): 3.56 (s, 3H), 3.99 (s, 3H), 4.25 (s, 2H), 7.19-7.48 (m, 4H), 12.40 (s, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 304.
Anal. Calcd. for $C_{12}H_{13}N_7OS$: C, 47.51; H, 4.32; N, 32.32; Found: C, 47.50; H, 4.32; N, 32.34.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(1-phenyl-1H-tetrazol-5-yl)thio]acetamide (2d)

^{1}H-NMR (400 MHz, DMSO-d_6): 3.54 (s, 3H), 4.34 (s, 2H), 7.19-7.71 (m, 9H), 12.40 (s, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 366. Anal. Calcd. for $C_{17}H_{15}N_7OS$: C, 55.88; H, 4.14; N, 26.83; Found: C, 55.89; H, 4.11; N, 26.85.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(benzimidazol-2-yl)thio]acetamide (2e)

^{1}H-NMR (400 MHz, DMSO-d_6): 3.53 (s, 3H), 4.34 (s, 2H), 6.90-7.66 (m, 8H), 12.60 (s, 1H), 12.80 (br, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 338.
Anal. Calcd. for $C_{17}H_{15}N_5OS$: C, 60.52; H, 4.48; N, 20.76; Found: C, 60.50; H, 4.49; N, 20.78.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(5-chlorobenzimidazol-2-yl)thio]acetamide (2f)

^{1}H-NMR (400 MHz, DMSO-d_6): 3.54 (s, 3H), 4.35 (s, 2H), 7.11-7.64 (m, 6H), 8.41 (s, 1H), 12.61 (s, 1H), 12.82 (br, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 372.
Anal. Calcd. for $C_{17}H_{14}ClN_5OS$: C, 54.91; H, 3.79; N, 18.83; Found: C, 54.90; H, 3.80; N, 18.80.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(5-nitrobenzimidazol-2-yl)thio]acetamide (2g)

^{1}H-NMR (400 MHz, DMSO-d_6): 3.57 (s, 3H), 4.35 (s, 2H), 7.14-8.07 (m, 6H), 8.28 (s, 1H), 12.62 (s, 1H), 12.83 (br, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 383.
Anal. Calcd. for $C_{17}H_{14}N_6O_3S$: C, 53.40; H, 3.69; N, 21.98; Found: C, 53.39; H, 3.68; N, 21.99.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(5-chlorobenzothiazol-2-yl)thio]acetamide (2h)

^{1}H-NMR (400 MHz, DMSO-d_6): 3.60 (s, 3H), 4.35 (s, 2H), 7.21-8.12 (m, 7H), 12.55 (s, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 389.
Anal. Calcd. for $C_{17}H_{13}ClN_4OS_2$: C, 52.50; H, 3.37; N, 14.41; Found: C, 52.52; H, 3.35; N, 14.40.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(5-methoxybenzothiazol-2-yl)thio]acetamide (2i)

^{1}H-NMR (400 MHz, DMSO-d_6): 3.60 (s, 3H), 3.83 (s, 3H), 4.34 (s, 2H), 6.99-7.87 (m, 7H), 12.56 (s, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 385.
Anal. Calcd. for $C_{18}H_{16}N_4O_2S_2$: C, 56.23; H, 4.19; N, 14.57; Found: C, 56.22; H, 4.20; N, 14.56.

N-(1-Methyl-1H-benzimidazol-2-yl)-2-[(5-chlorobenzoxazol-2-yl)thio]acetamide (2j)

^{1}H-NMR (400 MHz, DMSO-d_6): 3.56 (s, 3H), 4.31 (s, 2H), 7.08-7.74 (m, 7H), 12.50 (s, 1H).
MS (ESI) (*m/z*): $[M+1]^+$ 373.
Anal. Calcd. for $C_{17}H_{13}ClN_4O_2S$: C, 54.77; H, 3.51; N, 15.03; Found: C, 54.76; H, 3.50; N, 15.05.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-substitutedpiperazine-1-carbodithioate (2k-2u)

A mixture of 2-chloro-*N*-(1-methyl-1*H*-benzimidazol-2-yl)acetamide (**1**) (2 mmol) and appropriate sodium salt of *N*,*N*-disubstituted dithiocarbamic acid (2 mmol) in acetone (10 mL) was stirred at room temperature for 8 hours and filtered. The residue was washed with water and crystallized from ethanol.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-(2-hydroxyethyl)piperazine-1-carbodithioate (2k)

^{1}H-NMR (500 MHz, DMSO-d_6): 2.44 (2H, t, *J*=6.5 Hz, 6.0 Hz), 3.32-3.34 (4H, m), 3.53 (2H, t, *J*=6.0 Hz), 3.60 (3H, s), 3.97-4.26 (7H, m), 7.19-7.26 (2H, m), 7.44-7.49 (2H, m), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 394.
Anal. Calcd. for $C_{17}H_{23}N_5O_2S_2$: C, 51.89; H, 5.89; N, 17.80; Found: C, 51.90; H, 5.88; N, 17.80.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl4-(2-(dimethylamino)ethyl) piperazine-1-carbodithioate (2l)

^{1}H-NMR (500 MHz, DMSO-d_6): 2.14 (6H, s), 2.34-2.37 (4H, m), 2.42-2.45 (4H, m), 3.60 (3H, s), 3.96-4.26 (6H, m), 7.19-7.27 (2H, m), 7.45-7.50 (2H, m), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 421.
Anal. Calcd. for $C_{19}H_{28}N_6OS_2$: C, 54.26; H, 6.71; N, 19.98; Found: C, 54.25; H, 6.70; N, 19.98.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-(3-(dimethylamino)propyl) piperazine-1-carbodithioate (2m)

^{1}H-NMR (500 MHz, DMSO-d_6): 1.53-1.59 (2H, m), 2.10 (6H, s), 2.22 (2H, t, *J*=7.5 Hz, 7.0 Hz), 2.32 (2H, t, *J*=7.5 Hz), 2.45-2.46 (4H, m), 3.63 (3H, s), 3.97-4.26 (6H, m),

7.19-7.26 (2H, m), 7.45-7.50 (2H, m), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 435
Anal. Calcd. for $C_{20}H_{30}N_6OS_2$: C, 55.27; H, 6.96; N, 19.34; Found: C, 55.26; H, 6.95; N, 19.36.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-(pyrimidin-2-yl)piperazine-1-carbodithioate (2n)
^{1}H-NMR (500 MHz, DMSO-d_6): 3.60 (3H, s), 3.90-4.31 (8H, m), 6.70 (1H, t, *J*= 5.0 Hz, 4.5 Hz), 7.19-7.27 (2H, m), 7.45 (1H, d, *J*=7.5 Hz), 7.50 (1H, d, *J*=7.5 Hz), 8.41 (2H, d, *J*=5.0 Hz), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 428.
Anal. Calcd. for $C_{19}H_{21}N_7OS_2$: C, 53.38; H, 4.95; N, 22.93; Found: C, 53.39; H, 4.94; N, 22.94.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-phenylpiperazine-1-carbodithioate (2o)
^{1}H-NMR (500 MHz, DMSO-d_6): 3.31-3.33 (4H, m), 3.60 (3H, s), 4.10-4.40 (6H, m), 6.83 (1H, t, *J*=7.5 Hz, 7.0 Hz), 6.97 (2H, d, *J*=8.0 Hz), 7.21-7.27 (4H, m), 7.45-7.50 (2H, m), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 426.
Anal. Calcd. for $C_{21}H_{23}N_5OS_2$: C, 59.27; H, 5.45; N, 16.46; Found: C, 59.26; H, 5.44; N, 16.48.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-(4-fluorophenyl)piperazine-1-carbodithioate (2p)
^{1}H-NMR (500 MHz, DMSO-d_6): 3.31-3.34 (4H, m), 3.60 (3H, s), 4.14-4.37 (6H, m), 6.96-7.00 (2H, m), 7.05-7.11 (2H, m), 7.19-7.27 (2H, m), 7.45 (1H, d, *J*=7.5 Hz), 7.50 (1H, d, *J*=7.5 Hz), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 444
Anal. Calcd. for $C_{21}H_{22}FN_5OS_2$: C, 56.86; H, 5.00; N, 15.79; Found: C, 56.85; H, 5.02; N, 15.77.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-(4-nitrophenyl)piperazine-1-carbodithioate (2r)
^{1}H-NMR (500 MHz, DMSO-d_6): 3.60 (3H, s), 3.67-3.77 (4H, m), 4.21-4.31 (6H, m), 6.96 (2H, d, *J*=9.5 Hz), 7.20-7.27 (2H, m), 7.45 (1H, d, *J*=7.5 Hz), 7.50 (1H, d, *J*=7.5 Hz), 8.10 (2H, d, *J*=9.5 Hz), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 471
Anal. Calcd. for $C_{21}H_{22}N_6O_3S_2$: C, 53.60; H, 4.71; N, 17.86; Found: C, 53.59; H, 4.70; N, 17.85.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-(4-methoxyphenyl)piperazine-1-carbodithioate (2s)
^{1}H-NMR (500 MHz, DMSO-d_6): 3.12-3.18 (4H, m), 3.60 (3H, s), 3.70 (3H, s), 4.14-4.37 (6H, m), 6.85-6.87 (2H, m), 6.94-6.96 (2H, m), 7.20-7.29 (2H, m), 7.44-7.50 (2H, m), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 456
Anal. Calcd. for $C_{22}H_{25}N_5O_2S_2$: C, 58.00; H, 5.53; N, 15.37; Found: C, 58.02; H, 5.51; N, 15.36.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-benzylpiperazine-1-carbodithioate (2t)
^{1}H-NMR (500 MHz, DMSO-d_6): 2.46-2.48 (4H, m), 3.52-3.53 (2H, m), 3.66 (3H, s), 4.17-4.24 (6H, m), 7.08-7.13 (2H, m), 7.26-7.41 (7H, m), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 440
Anal. Calcd. for $C_{22}H_{25}N_5OS_2$: C, 60.11; H, 5.73; N, 15.93; Found: C, 60.10; H, 5.72; N, 15.92.

2-((1-Methyl-1H-benzimidazol-2-yl)amino)-2-oxoethyl 4-(4-methylbenzyl)piperazine-1-carbodithioate (2u)
^{1}H-NMR (500 MHz, DMSO-d_6): 2.29 (3H, s), 2.44-2.46 (4H, m), 3.48-3.50 (2H, m), 3.60 (3H, s), 4.26-4.30 (6H, m), 7.14 (2H, d, *J*=8.0 Hz), 7.17-7.25 (4H, m), 7.44 (1H, d, *J*=7.5 Hz), 7.49 (1H, d, *J*=7.5 Hz), 12.40 (1H, s).
MS (ESI) (*m/z*): $[M+1]^+$ 454
Anal. Calcd. for $C_{23}H_{27}N_5OS_2$: C, 60.90; H, 6.00; N, 15.44; Found: C, 60.91; H, 6.01; N, 15.45.

Microbiology

Antibacterial assay

Microbroth dilution method was carried out to evaluate antimicrobial activity of the compounds (**2a-u**) (23). Tested bacterial strains were *Micrococcus luteus* (NRLL B-4375), *Bacillus subtilis* (NRRL NRS-744),

Pseudomonas aeruginosa (ATCC 27853), *Staphylococcus aureus* (NRRL B-767), *Escherichia coli* (ATCC 25922), *Listeria monocytogenes* (ATCC 7644). The stock solutions of the samples were prepared in dimethyl sulfoxide (DMSO, Merck). Dilution series using sterile distilled water were prepared from 4 mg/mL to 0.0039 mg/mL in micro-test tubes that were transferred to 96-well microtiter plates as 100 µL. Overnight-grown bacterial suspensions in double-strength Mueller–Hinton Broth were standardized to 10^8 CFU/mL using McFarland No: 0.5 standard solutions. 100 µL of each microorganism suspension was then added into the wells. The last well-chain without a microorganism was used as a negative control. Sterile distilled water and the medium served as a positive growth control. After incubation at 37°C for 18-24 h, antimicrobial activity was detected by spraying of 0.5 % triphenyl tetrazolium chloride (TTC, Merck) aqueous solution.

Antifungal assay

The antifungal activities of the compounds (**2a-u**) were tested using the microbroth dilution method with some modifications (23, 24). Tested fungal strains were *Aspergillus parasiticus* (NRRL 465), *Aspergillus flavus* (NRRL 3537), *Aspergillus niger* (ATCC 1094), *Fusarium solani* (NRRL 13414), *Candida glabrata* (Clinical Isolate, Eskişehir Osmangazi University, Faculty of Medicine, Eskişehir, Turkey), *Candida tropicalis* (NRLL Y-12968), *Candida krusei* (NRLL Y-7179), *Candida parapsilosis* (NRLL Y-12696). The stock solutions of the samples were prepared in DMSO. Dilution series using sterile distilled water were prepared from 4 mg/mL to 0.0039 mg/mL in micro-test tubes that were transferred to 96-well microtiter plates as 100 µL. Filamentous fungal strains grown on Potato Dextrose Agar (PDA) at 25 ºC for 5 days were suspended in double-strength Potato Dextrose Broth (PDB) and then standardized to 10^5 spores/mL. Yeast strains grown on Sabouraud Dextrose Agar (SDA) at 37 ºC for overnight were suspended in double-strength Sabouraud Dextrose broth (SDB) and then standardized to 10^8 CFU/mL using McFarland No: 0.5 standard solutions. 100 µL of each cell suspension was then added into the wells. The last well-chain without a fungus was used as a negative control. Sterile distilled water and the medium served as a positive growth control. After incubation at 25 °C for filamentous fungi and 37 ºC for yeasts for 48-72 h, antifungal activity was detected by investigation of mycelia growing and turbidity under stereo microscope.

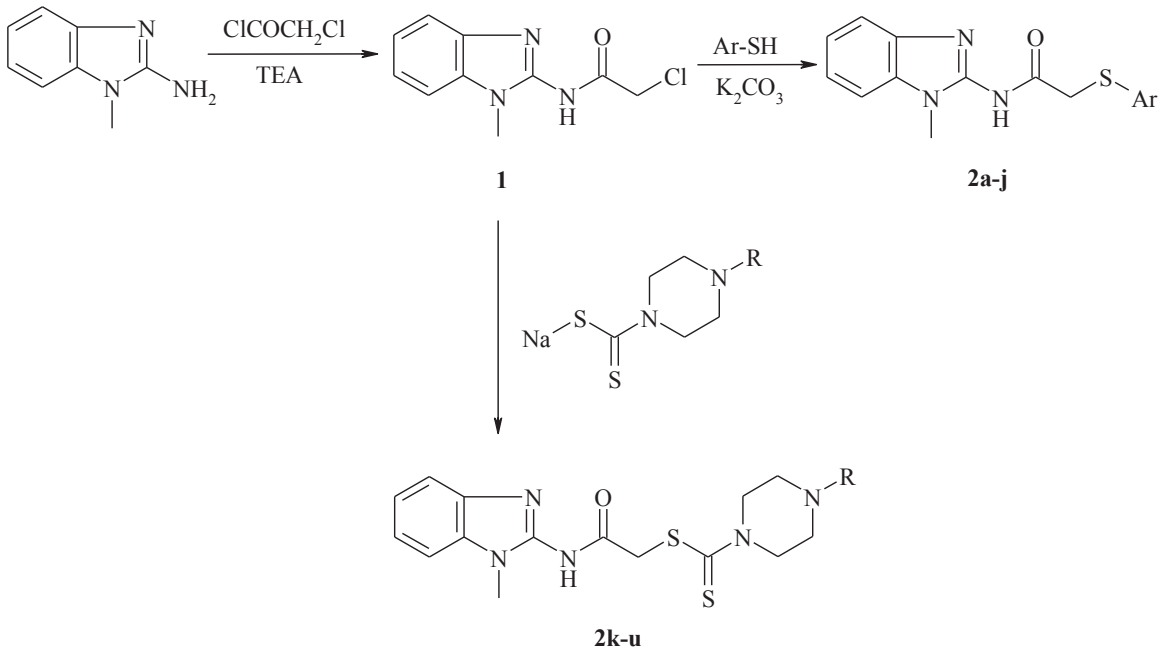
Minimum inhibitory concentration (MIC) was defined as the lowest concentration of a compound that inhibit the visible growth of a microorganism, as indicated by the TTC staining and investigation under stereo microscope. Streptomycin was used as a standard antibacterial agent, whereas ketoconazole was used as an antifungal agent.

RESULTS AND DISCUSSION

The synthesis of compounds **2a-u** followed the general pathway outlined in Scheme 1. Initially, 2-chloro-*N*-(1-methyl-1*H*-benzimidazol-2-yl)acetamide (**1**) was obtained by the reaction of 1-methyl-1*H*-benzimidazol-2-amine with chloroacetyl chloride in the presence of triethylamine.

N-(1-Methyl-1*H*-benzimidazol-2-yl)-2-(arylthio)acetamide derivatives (**2a-j**) and 2-((1-methyl-1*H*-benzimidazol-2-yl)amino)-2-oxoethyl 4-substitutedpiperazine-1-carbodithioate derivatives (**2k-2u**) were synthesized *via* the treatment of 2-chloro-*N*-(1-methyl-1*H*-benzimidazol-2-yl)acetamide (**1**) with aryl thiols and appropriate sodium salts of *N*,*N*-disubstituted dithiocarbamic acids, respectively. The spectral data and elemental analysis results of the synthesized compounds (**2a-u**) were in agreement with the proposed structures. Yields and melting points of the compounds are given in Table 1.

The compounds were tested *in vitro* against various pathogenic bacteria and fungi species. Among bacteria species, *P. aeruginosa* was the most susceptible bacterium to compounds **2b-2g.** These compounds and streptomycin exhibited the same level of antibacterial activity with a MIC value of 125 µg/mL, whereas other derivatives showed their antibacterial activity against *P. aeruginosa* with a MIC value of 250 µg/mL (Table 2).



Scheme 1. The synthetic route for the preparation of compounds **2a-u**.

Table 1. Yields and melting points of compounds **2a-u**

Compound	Ar	R	Yield (%)	M.p. (°C)
2a	4-Methyl-4*H*-1,2,4-triazol-3-yl	-	75	188
2b	5-Methyl-1,3,4-thiadiazol-2-yl	-	83	205
2c	1-Methyl-1*H*-tetrazol-5-yl	-	85	203
2d	1-Phenyl-1*H*-tetrazol-5-yl	-	82	212
2e	Benzimidazol-2-yl	-	79	146
2f	5-Chlorobenzimidazol-2-yl	-	84	158
2g	5-Nitrobenzimidazol-2-yl	-	87	177
2h	5-Chlorobenzothiazol-2-yl	-	78	231
2i	5-Methoxybenzothiazol-2-yl	-	73	208
2j	5-Chlorobenzoxazol-2-yl	-	77	333
2k	-	2-Hydroxyethyl	82	82
2l	-	2-(Dimethylamino)ethyl	76	76
2m	-	3-(Dimethylamino)propyl	67	67
2n	-	2-Pyrimidinyl	68	68
2o	-	Phenyl	78	78
2p	-	*p*-Fluorophenyl	65	65
2r	-	*p*-Nitrophenyl	77	77
2s	-	*p*-Methoxyphenyl	70	70
2t	-	Benzyl	75	75
2u	-	*p*-Methylbenzyl	71	71

Compounds **2p**, **2s**, **2t** and **2u** were the most effective anticandidal derivatives against *C. krusei* with a MIC value of 125 µg/mL when compared with ketoconazole (MIC= 62.5 µg/mL). Furthermore, compounds **2s** and **2u** showed the highest antifungal activity against *F. solani* with a MIC value of 125 µg/mL, whereas ketoconazole exhibited its antifungal activity with a MIC value of 62.5 µg/mL (Table 3).

It can be concluded that some arylthio-substituted derivatives (**2b-2g**) were more effective against *P. aeruginosa* than dithiocarbamate derivatives, whereas some dithiocarbamate-substituted derivatives (**2p, 2s, 2t** and **2u**) were more effective against *C. krusei* than arylthio-substituted derivatives.

CONCLUSION

In an effort to develop potent antimicrobial agents, we described the synthesis of a series of benzimidazole-based acetamide derivatives (**2a-u**) and focused on their *in vitro* antibacterial and antifungal effects.

Among these derivatives, arylthio-substituted compounds **2b-2g** can be identified as the most promising antibacterial agents against *P. aeruginosa* with a MIC value of 125 µg/mL when compared with streptomycin (MIC= 125 µg/mL). Dithiocarbamate-substituted compounds **2p**, **2s**, **2t** and **2u** exhibited the most potent antifungal activity against *C. krusei* with a MIC value of 125 µg/mL. Compounds **2s** and **2u** were also the most effective antifungal derivatives against *F. solani* with a MIC value of 125 µg/mL.

Table 2. Antibacterial activity of compounds **2a-u** as MIC values (µg/mL)

Compound	A	B	C	D	E	F
2a	250	250	250	250	250	250
2b	250	250	250	250	250	125
2c	250	250	500	250	500	125
2d	250	250	500	250	500	125
2e	250	250	250	250	250	125
2f	250	250	250	250	500	125
2g	250	250	250	125	250	125
2h	250	250	250	250	250	250
2i	250	250	250	250	250	250
2j	250	250	500	250	250	250
2k	250	250	250	125	250	250
2l	250	250	250	250	250	250
2m	250	250	250	250	250	250
2n	250	250	500	250	250	250
2o	250	250	250	250	250	250
2p	250	250	250	250	500	250
2r	250	250	250	250	250	250
2s	250	250	250	250	250	250
2t	250	250	250	250	250	250
2u	250	250	250	250	500	250
Streptomycin	7.81	15.625	15.625	31.25	31.25	125

A: *L. monocytogenes* (ATCC 7644), **B**: *M. luteus* (NRLL B-4375), **C**: *B. subtilis* (NRRL NRS-744), **D**: *E. coli* (ATCC 25922), **E**: *S. aureus* (NRRL B-767), **F**: *P. aeruginosa* (ATCC 27853).

Table 3. Antifungal activity of compounds **2a-u** as MIC values (μg/mL)

Compound	A	B	C	D	E	F	G	H
2a	250	250	250	250	250	250	250	250
2b	250	250	250	250	250	250	250	250
2c	250	250	250	250	250	250	250	250
2d	250	250	250	250	250	250	250	250
2e	250	250	250	250	250	250	250	250
2f	250	250	250	250	250	250	250	250
2g	250	250	250	250	250	250	250	250
2h	250	250	250	250	250	250	250	250
2i	250	250	250	250	250	250	250	250
2j	250	250	250	250	250	250	250	250
2k	250	250	250	250	250	250	250	250
2l	250	250	250	250	250	250	250	250
2m	250	250	250	250	250	250	250	250
2n	250	250	250	250	250	250	250	250
2o	250	250	250	250	250	250	250	250
2p	250	250	250	250	125	125	125	125
2r	250	250	250	250	250	250	250	250
2s	250	125	125	125	125	125	125	125
2t	250	250	250	250	125	125	125	125
2u	125	125	125	125	125	125	125	125
Ketoconazole	31.25	15.62	7.81	62.5	31.25	7.81	62.5	7.81

A: *A. niger* (ATCC 1095), **B**: *A. flavus* (NRRL 3537), **C**: *A. parasiticus* (NRRL 465), **D**: *F. solani* (NRRL 13414), **E**: *C. glabrata* (Clinical Isolate, Eskişehir Osmangazi University, Faculty of Medicine, Eskişehir, Turkey), **F**: *C. tropicalis* (NRLL Y-12968), **G:** *C. krusei* (NRLL Y-7179), **H:** *C. parapsilosis* (NRLL Y-12696).

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