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Synthesis of some pyridazine derivatives carrying urea, thiourea, and sulfonamide moieties and their antimicrobial activity

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Some pyridazine derivatives carrying urea, thiourea, and sulfonamide groups were synthesized and evaluated for their antimicrobial activity against gram-positive and gram-negative bacteria, and fungi by using broth microdilution. The structures of these new compounds were confirmed by ^{1}H-NMR, mass spectrum, and elemental analysis. The synthesized compounds exhibited generally promising inhibitory activity against *S. aureus* (MIC ranging from 2 to 4 μg/mL) and *E. coli* (MIC ranging from 4 to 16 μg/mL). Moreover, all compounds showed antifungal activity against both *C. albicans* and *C. parapsilosis*, with a MIC value of 8 μg/mL.

Key Words: Pyridazine derivatives, antibacterial activity, antifungal activity.

Introduction

Despite many significant progresses in antimicrobial therapy, infectious diseases caused by bacteria and fungi remain a major worldwide health problem due to rapid development of resistance to the existing antimicrobial drugs (antibacterial and antifungal). In other words, the increasing use and misuse of the existing antimicrobial drugs have resulted in the development of resistant pathogens.

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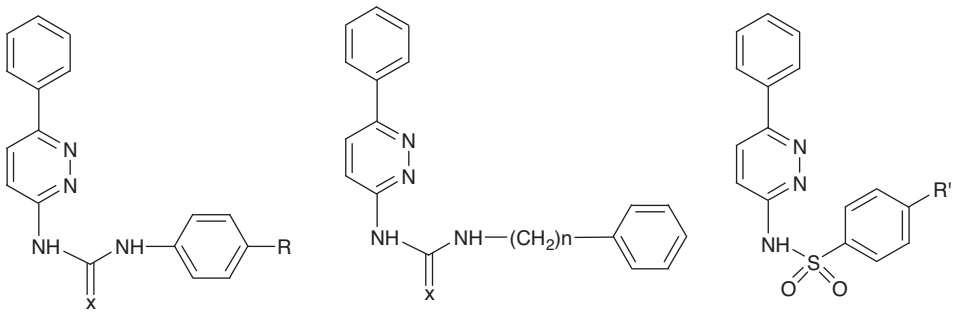
In particular, the emergence of multidrug resistant gram-positive and gram-negative bacteria has caused life-threatening infectious diseases in many countries around the world. For example, multidrug resistant gram-positive bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *S. aureus* (VRSA), and vancomycin-resistant Enterococci (VRE) are of major concern.[1] Similarly, gram-negative bacteria producing extended spectrum β-lactamase (ESβL) like *Escherichia coli* have also caused serious health problems.[1] In addition, systemic and dermal fungal infections have significantly increased, specifically in individuals with suppressed immune systems such as cancer chemotherapy and AIDS patients.[2] Although there are different antifungal drugs used in the treatment of fungal infections, some of them have undesirable side effects because of the biochemical similarity between human cell and fungi forms.[3] Moreover, some of them become less effective due to the development of resistance to these drugs.[3] Therefore, a number of clinically effective antibacterial and antifungal drugs have become less effective due to the development of resistance to these drugs.

As a result, there is an increasing need to design new antibacterial and antifungal agents with better activity profile and lower toxicity.

Many research groups as well as our group have been interested in pyridazine derivatives due to their diverse biological activities, including antimicrobial,[4–6] antioxidant,[7] analgesic, and anti-inflammatory.[8,9] On the other hand, urea and thiourea derivatives have been reported to have antimicrobial,[10] antiviral,[11,12] anti-HIV,[13,14] and antitumor[15,16] properties apart from other biological activities. As for sulfonamide derivatives, they are reported to possess different biological activities and some are used as drugs.[3,17]

On the basis of these findings, the aim of this study was to synthesize the hybrid molecules through the combination of different pharmacophores in one structure with the hope of obtaining better antibacterial and antifungal agents.

Therefore, we synthesized 16 new pyridazine derivatives carrying urea, thiourea, and sulfonamide groups at position 3 in order to investigate their antibacterial and antifungal activities.



X = O, S
n = 1, 2
R and R' = H, Cl, CH_3, OCH_3

Figure. General structure of the synthesized compounds.

Experimental

Chemistry

3-Chloro-6-phenylpyridazine was purchased from Maybridge (England). All the other chemicals used for the synthesis of the compounds were purchased from Aldrich (Germany) and Merck (Germany). Microwave irradiation was carried out in a microwave oven (Milestone-MicroSYNTH-Italy). Melting points of the compounds were recorded on an Electrothermal-9200 digital melting points apparatus and are uncorrected. The ^{1}H-NMR spectra were recorded with a Varian Mercury-400 FT-NMR spectrometer (Varian Inc., Palo Alto, CA, USA) in DMSO-d_6 at the Faculty of Pharmacy, Ankara University, Ankara, Turkey. The mass spectra were obtained on a Waters ZQ micromass LC-MS spectrometer (Waters Corporation, Milford, MA, USA) using the ESI(+) method at the Faculty of Pharmacy, Ankara University. Elemental analysis was performed on a Leco 932 CHNS instrument (St. Joseph, MI, USA) at the Faculty of Pharmacy, Ankara University, and the results were within $\pm 0.4\%$ of the theoretical values. 3-Amino-6-phenylpyridazine **(1)** used to synthesize the title compounds was prepared by Suzuki cross coupling reaction in our laboratory as described in the literature.[18]

General procedure for synthesis of (2a-2d)

The appropriate isocyanate derivatives (0.0022 mol) were added to a solution of the 3-amino-6-phenylpyridazine (0.002 mol) in 15 mL of toluene. The resulting mixture was heated under microwave irradiation at 120 °C (450 W) for 15 min. At the end of this period, the reaction mixture was evaporated to dryness and all urea derivatives were crystallized from acetic acid.

***N*-Phenyl-*N*'-(6-phenylpyridazin-3-yl)urea (2a)**

Yield: 38%; m.p.: 307 °C. ^{1}H-NMR (DMSO-d_6) δ: 9.85 (s, 1H), 9.76 (s, 1H), 8.22 (d, J=9.2 Hz, 1H), 8.15-8.03 (m, 3H), 7.56-7.47 (m, 5H), 7.34 (t, J=7.6 Hz, 2H), 7.05 (t, J=7.6 Hz, 1H). MS ESI(+) m/e291 (M+H,100). Anal. ($C_{17}H_{14}N_4O$): C, H, N calc. 70.33, 4.86, 19.30 found 70.22, 4.58, 19.03.

***N*-(4-Chlorophenyl)-*N*'-(6-phenylpyridazin-3-yl)urea (2b)**

Yield: 45%; m.p.: 298 °C. ^{1}H-NMR (DMSO-d_6) δ: 9.88 (s, 1H), 9.86 (s, 1H), 8.22 (d, J=9.2 Hz, 1H), 8.13-8.08 (m, 3H), 7.56-7.49 (m, 5H), 7.38 (d, J=8.8 Hz, 2H). MS ESI(+) m/e325 (M+H, 100). Anal. ($C_{17}H_{13}ClN_4O$): C, H, N calc. 62.87, 4.03, 17.25 found 63.24, 4.16, 17.22.

***N*-(4-Methylphenyl)-*N*'-(6-phenylpyridazin-3-yl)urea (2c)**

Yield: 33%; m.p.: 287 °C. ^{1}H-NMR (DMSO-d_6) δ: 9.83 (s, 1H), 9.70 (s, 1H), 8.22 (d, J=9.2 Hz, 1H), 8.12-8.08 (m, 3H), 7.56-7.49 (m, 3H), 7.40 (d, J=8 Hz, 2H), 7.14 (d, J=8 Hz, 2H), 2.27 (s, 3H). MS ESI(+) m/e305 (M+H, 100). Anal. ($C_{18}H_{16}N_4O$): C, H, N calc. 71.04, 5.30, 18.41 found 71.31, 4.92, 18.19.

***N*-(4-Methoxyphenyl)-*N*'-(6-phenylpyridazin-3-yl)urea (2d)**

Yield: 30%; m.p.: 270 °C. ^{1}H-NMR (DMSO-d_6) δ: 9.79 (s, 1H), 9.65 (s, 1H), 8.22 (d, J=9.2 Hz, 1H), 8.10-8.08 (m, 3H), 7.55-7.49 (m, 3H), 7.42 (d, J=7.2 Hz, 2H), 6.92 (d, J=7.2 Hz, 2H), 3.74 (s, 3H). MS ESI(+) m/e321 (M+H, 100). Anal. ($C_{18}H_{16}N_4O_2$): C, H, N calc. 67.49, 5.03, 17.49 found 67.64, 4.70, 17.28.

***N*-Benzyl-*N*'-(6-phenylpyridazin-3-yl)urea (2e)**

Yield: 30%; m.p.: 268 °C. ^{1}H-NMR (DMSO-d_6) δ: 9.76 (s, 1H), 9.65 (s, 1H), 8.16 (d, J=9.2 Hz, 1H), 8.05 (d, J=7.2 Hz 2H), 7.94 (d, J=9.2 Hz, 1H), 7.54-7.25 (m, 8H), 4.43 (s, 2H). MS ESI(+) m/e305 (M+H, 100). Anal. ($C_{18}H_{16}N_4O$): C, H, N calc. 71.04, 5.30, 18.41 found 71.19, 5.11, 18.24.

***N*-(2-Phenylethyl)-*N*'-(6-phenylpyridazin-3-yl)urea (2f)**

Yield: 25%; m.p.: 216 °C. ^{1}H-NMR (DMSO-d_6) δ: 9.76 (s, 1H), 9.65 (s, 1H), 8.12 (d, J=9.2 Hz, 1H), 8.05 (d, J=7.2 Hz, 2H), 7.94 (d, J=9.2 Hz, 1H), 7.54-7.19 (m, 8H), 3.45 (t, J=7.2 Hz 2H), 2.81 (t, J=7.2 Hz, 2H). MS ESI(+) m/e319 (M+H,100). Anal. (C_{19} H_{18} N_4 O): C, H, N calc. 71.68, 5.70, 17.60 found 71.35, 5.90, 17.41.

General procedure for synthesis of (3a-3d)

The appropriate isothiocyanate derivatives (0.0022 mol) were added to a solution of the 3-amino-6-phenylpyridazine (0.002 mol) in 15 mL of toluene. The resulting mixture was heated under microwave irradiation at 120 °C (450 W) for 20 min. At the end of this period, the reaction mixture was evaporated to dryness and all thiourea derivatives were crystallized from butanol.

***N*-Phenyl-*N*'-(6-phenylpyridazin-3-yl)thiourea (3a)**

Yield 35%; m.p.: 198 °C. ^{1}H-NMR (DMSO-d_6) δ: 13.52 (s, 1H), 11.19 (s, 1H), 8.34 (d, J=9.6 Hz, 1H), 8.10 (d, J=6.4 Hz, 2H), 7.71-7.52 (m, 6H), 7.44 (t, J=8 Hz, 2H), 7.28 (t, J=8 Hz, 1H). MS ESI(+) m/e307 (M+H, 100). Anal. ($C_{17}H_{14}N_4S$): C, H, N, S calc. 66.64, 4.61, 18.29, 10.47 found 66.76, 4.76, 18.12, 10.35.

***N*-(4-Chlorophenyl)-*N*'-(6-phenylpyridazin-3-yl)thiourea (3b)**

Yield 38%; m.p.: 200 °C. ^{1}H-NMR (DMSO-d_6) δ: 13.53 (s, 1H), 11.25 (s, 1H), 8.33 (d, J=9.6 Hz, 1H), 8.10 (d, J=6.4 Hz, 2H), 7.75-7.48 (m, 8H). MS ESI(+) m/e341 (M+H, 100). Anal. ($C_{17}H_{13}ClN_4S$): C, H, N, S calc. 59.91, 3.84, 16.44, 9.41 found 60.30, 3.94, 16.46, 9.25.

***N*-(4-Methylphenyl)-*N*'-(6-phenylpyridazin-3-yl)thiourea (3c)**

Yield 32%; m.p.: 199 °C. ^{1}H-NMR (DMSO-d_6) δ: 13.44 (s, 1H), 11.14 (s, 1H), 8.33 (d, J=9.6 Hz, 1H), 8.10 (d, J=6.4 Hz, 2H), 7.70 (d, J=9.6 Hz, 1H), 7.57-7.52 (m, 5H), 7.23 (d, J=8 Hz, 2H), 2.34 (s, 3H). MS ESI(+) m/e321 (M+H, 100). Anal. ($C_{18}H_{16}N_4S$): C, H, N, S calc. 67.47, 5.03, 17.49, 10.01 found 67.36, 5.16, 17.44, 9.93.

_N_-(4-Methoxyphenyl)-_N_'-(6-phenylpyridazin-3-yl)thiourea (3d)

Yield 30%; m.p.: 208 °C. ^{1}H-NMR (DMSO-d_6) δ: 13.32 (s, 1H), 11.13 (s, 1H), 8.33 (d, J=9.6 Hz, 1H), 8.10 (d, J=6.4 Hz, 2H), 7.70 (d, J=9.6 Hz, 1H), 7.60-7.52 (m, 5H), 6.99 (d, J=8 Hz, 2H), 3.79 (s, 3H). MS ESI(+) m/e337 (M+H, 100). Anal. ($C_{18}H_{16}N_4OS$): C, H, N, S calc. 64.26, 4.79, 16.65, 9.53 found 64.61, 4.73, 16.70, 9.43.

_N_-Benzyl-_N_'-(6-phenylpyridazin-3-yl)thiourea (3e)

Yield 30%; m.p.: 217 °C. ^{1}H-NMR (DMSO-d_6) δ: 11.92 (s, 1H), 10.97 (s, 1H), 8.24 (d, J=9.6 Hz, 1H), 8.03 (d, J=6.4 Hz, 2H), 7.59-7.27 (m, 9H), 4.95 (s, 2H). MS ESI(+) m/e321 (M+H, 100). Anal. ($C_{18}H_{16}N_4S$): C, H, N, S calc. 67.47, 5.03, 17.49, 10.01 found 67.65, 5.20, 17.36, 9.97.

_N_-(2-Phenylethyl)-_N_'-(6-phenylpyridazin-3-yl)thiourea (3f)

Yield: 25%; m.p.: 258 °C. ^{1}H-NMR (DMSO-d_6) δ: 11.62 (s, 1H), 10.80 (s, 1H), 8.24 (d, J=9.6 Hz, 1H), 8.03 (d, J=6.4 Hz, 2H), 7.59-7.20 (m, 9H), 3.90 (t, J=7.2 Hz, 2H), 2.99 (t, J=7.2 Hz, 2H). MS ESI(+) m/e335 (M+H, 100). Anal. (C_{19} H_{18} N_4 S): C, H, N, S calc. 68.23, 5.42, 16.75, 9.59 found 62.22, 5.70, 16.59, 9.71.

General procedure for synthesis of (4a-4d)

Substituted benzenesulfonyl chlorides (0.003 mol) were added to the solution of 3-amino-6-phenylpyridazine (0.003 mol) in 10 mL of pyridine at 0 °C. The resulting mixture was stirred at room temperature for 4 h. At the end of this period, the reaction mixture was poured into ice water. The precipitate was filtered and dried. After that, all sulfonamide derivatives were crystallized from isopropyl alcohol.

_N_-(6-Phenylpyridazin-3-yl)benzenesulfonamide (4a)

Yield 80%; m.p.: 204 °C. ^{1}H-NMR (DMSO-d_6) δ: 8.27 (d, J=10 Hz, 1H), 7.89-7.47 (m, 11H). MS ESI(+) m/e312 (M+H, 100). Anal. ($C_{16}H_{13}N_3O_2S$): C, H, N, S calc. 61.72, 4.21, 13.50, 10.30 found 61.90, 4.19, 13.45, 10.30.

4-Chloro-_N_-(6-phenylpyridazin-3-yl)benzenesulfonamide (4b)

Yield 85%; m.p.: 209 °C. ^{1}H-NMR (DMSO-d_6) δ: 8.33 (d, J=10 Hz, 1H), 7.92-7.51 (m, 10H). MS ESI(+) m/e346 (M+H, 100). Anal. ($C_{16}H_{12}ClN_3O_2S$): C, H, N, S calc. 55.57, 3.50, 12.15, 9.27 found 55.74, 3.60, 12.09, 9.24.

4-Methyl-_N_-(6-phenylpyridazin-3-yl)benzenesulfonamide (4c)

Yield 75%; m.p.: 194 °C. ^{1}H-NMR (DMSO-d_6) δ: 8.28 (d, J=10 Hz, 1H), 7.91-7.50 (m, 8H), 7.35 (d, J=8 Hz, 2H), 2.35 (s, 3H). MS ESI(+) m/e326 (M+H, 100). Anal. ($C_{17}H_{15}N_3O_2S$): C, H, N, S calc 62.75, 4.65, 12.91, 9.85 found 62.95, 4.60, 12.91, 9.88.

4-Methoxy-*N*-(6-phenylpyridazin-3-yl)benzenesulfonamide (4d)

Yield 75%; m.p.: 165 °C. ^{1}H-NMR (DMSO-d$_6$) δ: 8.24 (d, J=10 Hz, 1H), 7.89-7.47 (m, 8H), 7.04 (d, J=8.6 Hz, 2H), 3.78 (s, 3H). MS ESI(+) m/e342 (M+H, 100). Anal. ($C_{17}H_{15}N_3O_3S$): C, H, N, S calc 59.81, 4.43, 12.31, 9.39 found 59.88, 4.34, 12.25, 9.45.

Antimicrobial activity[19,20]

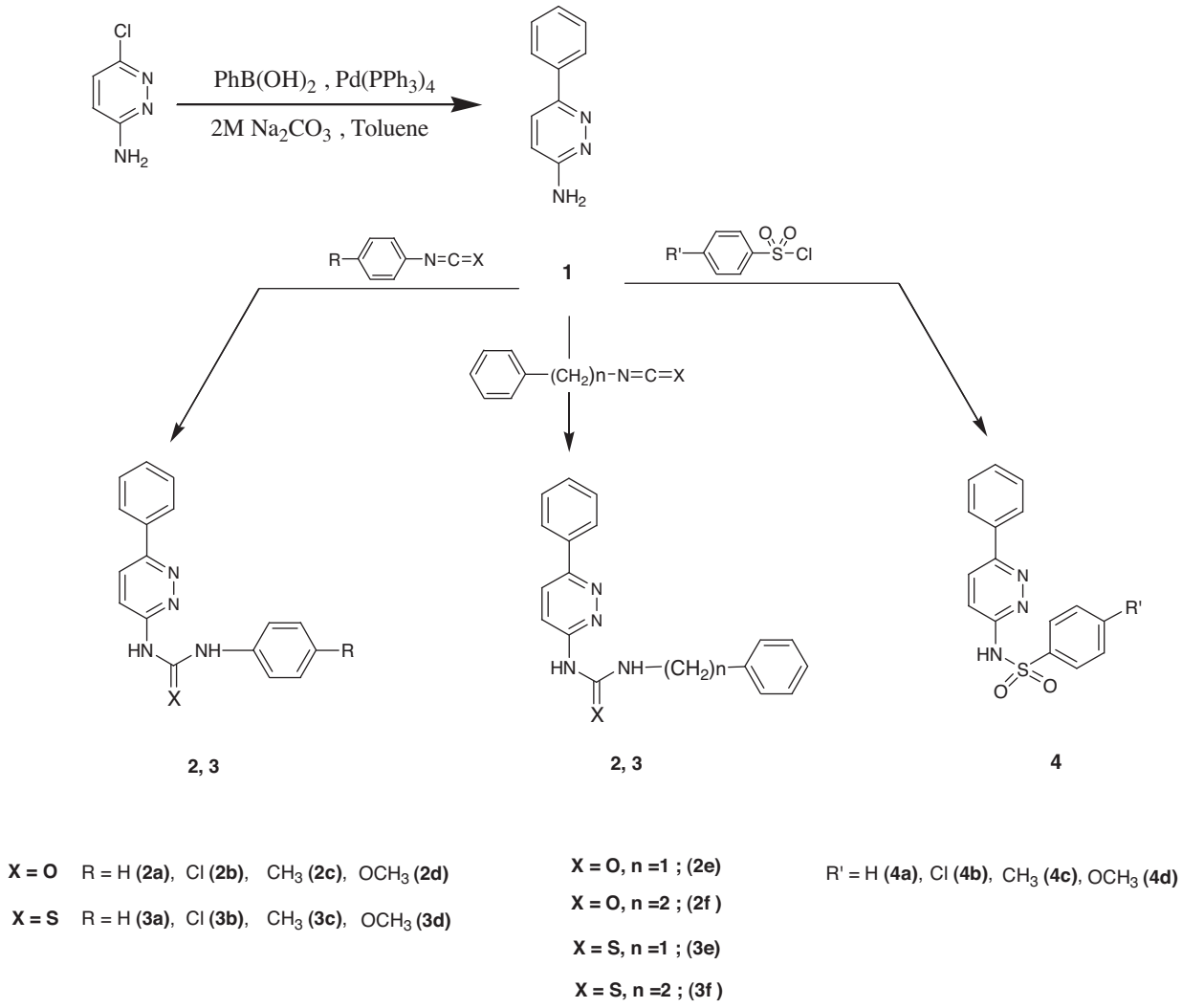
Minimum inhibitory concentration (MIC) values for the synthesized compounds were determined by using broth microdilution. Standard and the isolated strains of the bacteria;. *coli* ATCC 25922, *E. coli* producing extended spectrum β-lactamase (ESβL), *P. aeruginosa* ATCC 27853, *P. aeruginosa* isolate *S. aureus* ATCC 29213, methicillin-resistant *S. aureus* (MRSA), *Enterococcus faecalis* ATCC 29212, and *E. faecalis* isolate were used to determine antibacterial activity. As for antifungal activity, standard strains of *Candida albicans* ATCC 10231 and *Candida parapsilosis* ATCC 90018 were used. Ampicillin and fluconazole were used as references. All bacteria were cultivated in Mueller–Hinton Agar and were diluted with Mueller–Hinton Broth (Oxoid). All fungi were cultivated in Sabouraud Dextrose Agar. The fungi inoculums were prepared in Sabouraud liquid medium (Oxoid), which had been kept at 36 °C overnight, and were diluted with RPMI-1640 medium with L-glutamine buffered with 3-[N-morpholino]-propansulfonic acid (MOPS) at pH 7. The synthesized compounds and references were dissolved in DMSO/H_2O (50%), at a concentration of 1024 μg/mL. Two-fold dilutions of the synthesized compounds and reference compounds were added to the wells (512, 256. . . . . ..0.25 μg/mL). After that, suspension of the microorganisms was inoculated into all the wells. Final inoculum concentrations were 10^4 cfu/mL for bacteria and 2.5×10^3 cfu/mL for fungi in the wells. The sealed microplates were incubated at 36 °C for 24 h for antibacterial activity and at 36 °C for 48 h for antifungal activity in a humid chamber. At the end of the incubation period, MIC values were recorded as the lowest concentrations of the substances that had no visible turbidity.

Results and discussion

Chemistry

3-Amino-6-phenylpyridazine **(1)** used to synthesize the title compounds was prepared by Suzuki cross coupling reaction in our laboratory as described in the literature.[18] The urea **(2a-2f)** and thiourea derivatives **(3a-3f)** were obtained by the reaction of 3-amino-6-phenylpyridazine with the appropriate isocyanates and isothiocyanates respectively by microwave synthesis in toluene. The sulfonamide derivatives **(4a-4d)** were synthesized by the reaction of 3-amino-6-phenylpyridazine with the appropriate benzenesulfonyl chlorides in pyridine.

Synthetic route of the compounds is given in the Scheme. The chemical structures of the title compounds were elucidated by ^{1}H-NMR, mass spectrum, and elemental analysis. The ^{1}H-NMR, mass spectra, and elemental analysis data are in agreement with the proposed structures. In the ^{1}H-NMR spectra, the N-H protons of the urea **(2a-2f)** and thiourea **(3a-3f)** derivatives were observed as 2 separate singlets at 9.88-9.65 and 13.53-10.80 ppm, respectively. However, the N-H protons of the sulfonamide derivatives **(4a-4d)** were not seen in the ^{1}H-NMR spectrum; this may be attributed to the deuterium exchange.



Scheme. Synthetic route of the synthesized compounds.

Antimicrobial Activity

The synthesized compounds were tested for antibacterial activity against gram-negative *E. coli*, *E. coli* producing extended spectrum β-lactamase, *P. aeruginosa*, *P. aeruginosa* isolate, gram-positive *S. aureus*, methicillin-resistant *S. aureus* (MRSA, isolate), *E. faecalis*, and *E. faecalis* isolate bacteria, and for antifungal activity against *C. albicans* and *C. parapsilosis* by using broth microdilution. Ampicillin and fluconazole were used as antibacterial and antifungal references, respectively.

As shown in the Table, the synthesized compounds exhibited a broad spectrum of activity with MIC values 2-128 μg/mL against both gram-positive and gram-negative bacteria. Generally, synthesized compounds were more active against gram-positive bacteria rather than gram-negative bacteria. Apart from *E. coli* isolate, the title compounds were not active against the other bacteria isolates. Among the gram-positive bacteria tested, *S. aureus* showed relative high sensitivity towards the title compounds. Compounds **2a**, **2d**, and **2e**,

which are urea derivatives, and compounds **3b** and **3e**, which are thiourea derivatives, gave the best inhibitory activity against *S. aureus* with a MIC value of 2 μg/mL; that is, their antibacterial activity was 50% of that of ampicillin against *S. aureus*. Compounds **2a**, **2d**, **2e, 3b**, and **3e** may be worth studying further to develop better antibacterial agents against *S. aureus*. Further substitution on the pyridazine ring can be studied for these compounds. Antibacterial activity for the rest of the compounds was observed against *S. aureus* at 4 μg/mL concentration. The compounds showed activity against *E. faecalis* with MIC values of 4 and 8 μg/mL. Regarding the antibacterial activity of the target compounds against gram-negative bacteria, they exerted a relatively good inhibitory profile against *E. coli*, with MIC values ranging from 4 to 16 μg/mL. The antibacterial activity of compounds **2a-2c, 3b-3d**, and **4a-4c** was 50% of that of ampicillin against *E. coli*. Therefore, it can be suggested that these compounds show promise as antibacterial against *E. coli*. With respect to antifungal activity of the synthesized compounds, all compounds displayed antifungal activity against both *C. albicans* and *C. parapsilosis*, with a MIC value of 8 μg/mL. In other words, their antibacterial activity was 25% and 50% of that of fluconazole against *C. albicans* and *C. parapsilosis*, respectively. According to the obtained results, one can say that structural differences do not play a critical role in antifungal activity.

Table. Antimicrobial activity of the synthesized compounds (MICs, μg/mL).

Comp.	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**J**
2a	2	128	4	128	4	32	128	128	8	8
2b	4	128	8	128	4	32	128	128	8	8
2c	4	128	8	128	4	32	128	128	8	8
2d	2	128	4	128	16	64	128	128	8	8
2e	2	128	4	128	16	64	128	128	8	8
2f	4	128	8	128	16	64	128	128	8	8
3a	4	128	8	128	8	32	128	128	8	8
3b	2	128	8	128	4	32	128	128	8	8
3c	4	128	8	128	4	32	128	128	8	8
3d	4	128	8	128	4	32	128	128	8	8
3e	2	128	8	128	16	64	128	128	8	8
3f	4	128	4	128	16	32	128	128	8	8
4a	4	128	8	128	4	32	128	128	8	8
4b	4	128	4	128	4	32	128	128	8	8
4c	4	128	4	128	4	32	128	128	8	8
4d	4	128	4	128	16	64	128	128	8	8
AMP	1	128	0.5	128	2	128	128	128	-	-
FLU	-	-	-	-	-	-	-	-	2	4

AMP: ampicillin, FLU: fluconazole

A: *S. aureus* ATCC 29213, B: MRSA, C: *E. faecalis* ATCC 29212, D: *E. faecalis* isolate, E: *E.coli* ATCC 25922,

F: *E. coli* isolate, G: *P. aeruginosa* ATCC 27853,

H: *P. aeruginosa* isolate, I: *C. albicans* ATCC 10231, J: *C. parapsilosis* ATCC 90018

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