INTRODUCTION

The discovery of powerful and reliable antimicrobial agents has become an undeniably health care service with the knowledge and technology that humanity has acquired since the beginning of history. The increase to accessibility of these agents has rapidly reduced morbidity and mortality rates caused by several fatal diseases (Rice, 2008). Despite all that, today, we are still at war with opportunistic microorganisms. Yet, it seems that war will never end due to the increased resistance of bacteria and fungi (Pieczonka et al., 2013).

The first report about antimicrobial resistance was published in the 1940s. And today, the antimicrobial resistance has become a worldwide problem. Because of this problem, there is a need to develop new drugs. That’s why we synthesized some novel thiazolidine-4-one derivatives and evaluated their antimicrobial activity. The final compounds were obtained by reacting 2-[4,5-diphenylthiazol-2-yl]iminothiazolidin-4-one with some aryl aldehydes. The synthesized compounds were investigated for their antimicrobial activity against four Candida species, five gram-negative and four gram-positive bacterial species. The lead compounds (4a-h) were obtained with a yield of at least 70%. All compounds showed antimicrobial activity. Compound 4f (MIC: 31.25 µg/ml) exhibited more efficacy than the other compounds against C. glabrata (ATCC 24433). Compound 4b (MIC: 62.5 µg/ml) was the most active compound against all bacterial species, particularly K. pneumoniae (NCTC 9633). Whereas, compound 4c (MIC: <3.125 µg/ml) was observed as the most active compound against E. coli (ATCC 25922). In general, all compounds (4a-4h) showed antimicrobial activity against all fungi and bacterial species. Compounds 4b (2,6-dichlorobenzylidene), 4c (2,6-dihydroxybenzylidene), 4f (1H-pyrrol-2-yl)methylene), 4g (4-trifluoromethylbenzylidene) and 4h (2,3,4-trimethoxybenzylidene) were determined as the most active compounds.

Keywords: Thiazole. Thiazolidin-4-one. Azoles. Antibacterial activity. Anticandidal activity.
decades, depending on antibiotics misuse, clinically important bacteria were characterized not only by a single drug resistance, but also by multiple antibiotic resistance (Berber, Cokmus, Atalan, 2003; Levy, Marshall, 2004; Mitscher et al., 1999).

Although Candida species are existing as commensal flora in most of healthy people, they can cause various infections in humans. These infections can range from common simple to life-threatening serious diseases. Over the past two decades, the incidence of serious infections caused by opportunistic fungi have been increased in cancer and transplant patients (Chimenti et al., 2011; Muñoz-Bonilla, Fernández-Garcia, 2012; Rossello et al., 2002; Secci et al., 2012). As stated in several reports, the real problem is the inability to keep them under control, and for this reason the main goal of current efforts is to stop the increasing resistance against chemical agents (Bondock, Naser, Ammar, 2013; Rostom et al., 2009; Secci et al., 2012). Therefore, some urgent studies focused on blocking the development of resistance, breaking the developing resistance and/or finding new active compounds against the pathogens.

As a distinctive heterocyclic, thiazole ring takes a momentous place in modern medicinal chemistry. Different drug molecules, which have thiazole moiety, were observed to have the ability to exhibit various biological activities such as antitumor (Shi et al., 1996), antiviral (Kulabaş et al., 2017), antifungal (Fahmy, 2001), antibacterial (Kaspady et al., 2009), and antiallergic effects (Hargrave, Hess, Oliver, 1983). In addition, they display DNA gyrase (Tomasic et al., 2017), renin (Patt et al., 1992) and COX (Abdelazeem et al., 2017) inhibitor activities. Also, thiazole nucleus is presented in condensed state with other cyclic rings as in penicillin G (Lamotte, Dive, Ghysen, 1991). It also exists as non-condensed form in abafungin (Kumawat, 2018), febuxostat (Khosravan et al., 2008), cefdinir (Mine et al., 1988), thiamine, and SNS032 (Chhabria et al., 2016). Some of these drugs are extremely prescribed by physicians at the present time (Baumann et al., 2011).

The reduced forms of thiazole, thiazoline and thiazolone, have fascinated a great deal of interest due to their various synthetic and biological significances mentioned above. Indeed, 2-(N-substituted amino) thiazole and 2-(substituted imino]-1,3-thiazolidin-4-one derivatives have proven their key role in antimicrobial activity (Gürsoy, Terzioglu, Ötük, 1997; Rawal et al., 2007; Vicini et al., 2006). As attachment, 2-(substituted imino)thiazolidin-4-one or its tautomeric form 2-(substituted amino)thiazol-4(5H)-one come into prominence in medicinal chemistry for two significant reasons. Firstly, substitutions at the 2nd, 3rd and 5th positions may be diverse, but the major differences in structure and properties are revealed by the group attached to the carbon atom at the 2nd position. Secondly, the variations in methylene carbon-dependent substitutions are numerous and can be achieved through simple synthesis routes (Gzella et al., 2014; Metwally, Farahat, Abdel-Wahab, 2010; Tripathi et al., 2014).

In view of the consequences, the aim of this study was to synthesize some new thiazole-thiazolidin-4-one derivatives and investigate antimicrobial activity of lead compounds. Novel thiazole-thiazolidine-4-one derivatives (4a-4h) were acquired using intermediate product 2-[(4,5-diphenylthiazol-2-yl)imino]thiazolidin-4-one. The structural elucidation of the compounds was performed by 1H-NMR, 13C-NMR and LC-MS/MS spectral data and elemental analyses.

MATERIAL AND METHODS

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 reactions were monitored by thin-layer chromatography (TLC) using Silica Gel 60 F254 TLC plates (Merck KGaA, Darmstadt, Germany). All melting points (m.p.) were determined by MP90 digital melting point apparatus (Mettler Toledo, Ohio, USA) and were uncorrected. Spectroscopic data were recorded with the following instruments: 1H-NMR (nuclear magnetic resonance) Bruker DPX 300 FT-NMR spectrometer; 13C-NMR, Bruker DPX 75 MHz spectrometer (Bruker Bioscience, Billerica, MA, USA) and M+1 peaks were determined by Shimadzu 8040 LC/MS/MS system.
Synthesis of New Thiazole Derivatives Bearing Thiazolidin-4(5H)-One Structure and Evaluation of Their Antimicrobial Activity

(Shimadzu, Tokyo, Japan). Elemental analyses were performed on a Leco 932 CHNS analyzer (Leco, Michigan, USA).

**General procedure for the synthesis of the compounds 4,5-diphenylthiazol-2-amine (1)**

2-Bromo-1,2-diphenylethan-1-one and equal mole thiourea were dissolved in ethanol. The mixture was stirred for 6 hours. Thin-layer chromatography (TLC) was used to determine completion of the reaction.

**General procedure for the synthesis of the compounds 2-chloro-N-(4,5-diphenylthiazol-2-yl)acetamide (2)**

4,5-Diphenylthiazol-2-amine (0.02 mol, 5.05 g) and triethylamine (0.024 mol, 3.35 mL) were dissolved in THF with a constant mixing at 0–5°C, then chloroacetyl chloride (0.024 mol, 1.91 mL) was added dropwise gradually to this solution. The reaction mixture thus obtained was further stirred for 2 h at room temperature. After the solvent was vaporized to dryness, the remaining raw product was washed with water and filtered. Finally, the core product was recrystallized from ethanol.

**General procedure for the synthesis of the compounds 2-[(4,5-diphenylthiazol-2-yl)imino]thiazolidin-4-one (3)**

2-Chloro-N-(4,5-diphenylthiazol-2-yl)acetamide (0.017 mol, 5.59 g) and sodium thiocyanate (0.017 mol, 1.378 g) were degraded in ethanol. The reaction was refluxed for 6 hours. Thin-layer chromatography (TLC) was used to determine completion of the reaction.

**5-Substituted-2-[(4,5-diphenylthiazol-2-yl)imino]thiazolidin-4-one derivatives (4a-h)**

2-[(4,5-Diphenylthiazol-2-yl)imino]thiazolidin-4-one (0.99 mmol, 0.35 g) and aryl aldehyde derivatives (1.485 mmol) were solved in adequate acetic acid. For catalysis, ammonium acetate (1.98 mmol, 0.153 g) was added to the mixture. After refluxing with stirring for 6 hours, the reaction was checked with TLC. Finally, the reaction was ended, and the mixture was treated with water. Then, precipitated portion was filtered off. The final products were recrystallized from ethanol.

The same synthetic route described in previous study (Abdelazeem, Salama, Maghrabi, 2015).

5-(2,3-Dichlorobenzylidene)-2-[(4,5-diphenylthiazol-2-yl)imino]-1,3-thiazolidin-4-one (4a)

m. p. 296°C, ¹H-NMR (300 MHz, DMSO-d₆, ppm) δ 7.31-7.33 (m, 3H, Ar-H), 7.38-7.40 (m, 5H, Ar-H), 7.47-7.50 (m, 2H, Ar-H), 7.55-7.60 (m, H, Ar-H), 7.70 (s, H, Ar-H), 7.77 (d, J= 7.80 Hz, H, Ar-H), 7.84 (s, H, C=C-H), 12.95 (brs, H, N-H). ¹³C-NMR (75 MHz, DMSO-d₆, ppm) δ 127.53, 128.27, 128.56, 128.74, 128.88, 129.11, 129.53, 129.85, 132.23 (C=C-H), 166.80 (C=O). For C₂₅H₁₅Cl₂N₃OS₂ calculated: Elemental Analysis: C, 59.06%; H, 2.97%; N, 8.26%; found: C, 59.04%; H, 2.95%; N, 8.29%. HRMS (m/z): [M+H]⁺ calculated for C₂₅H₁₅Cl₂N₃OS₂: 508.0106; found: 508.0108.

5-(2,6-Dichlorobenzylidene)-2-[(4,5-diphenylthiazol-2-yl)imino]-1,3-thiazolidin-4-one (4b)

m. p. 257°C, ¹H-NMR (300 MHz, DMSO-d₆, ppm) δ 7.21-7.26 (m, 2H, Ar-H), 7.31-7.38 (m, 8H, Ar-H), 7.50 (t, J=8.03 Hz, H, Ar-H), 7.62 (d, J=7.88 Hz, 2H, Ar-H), 7.68 (s, H, C=C-H), 12.90 (brs, H, N-H). ¹³C-NMR (75 MHz, DMSO-d₆, ppm) δ 127.81, 128.52, 128.64, 128.74, 129.02, 129.20, 129.47, 129.81, 131.63, 132.03, 132.19, 133.47, 133.71, 134.42 (C=C-H), 146.38, 155.71, 165.98, 166.22 (C=O). For C₂₅H₁₅Cl₂N₃OS₂ calculated: Elemental Analysis: C, 59.06%; H, 2.97%; N, 8.26%; found: C, 59.09%; H, 2.94%; N, 8.28%. HRMS (m/z): [M+H]⁺ calculated for C₂₅H₁₅Cl₂N₃OS₂: 508.0106; found: 508.0108.

5-(3,4-Dihydroxybenzylidene)-2-[(4,5-diphenylthiazol-2-yl)imino]-1,3-thiazolidin-4-one (4c)

m. p. 237°C, ¹H-NMR (300 MHz, DMSO-d₆, ppm) δ 6.92 (d, J=8.24 Hz, H, Ar-H), 7.03-7.07 (m, H, Ar-H), 7.14 (s, H, Ar-H), 7.40 (s, 6H, Ar-H), 7.47-7.50 (m,
H, Ar-H), 7.58 (s, 3H, Ar-H), 7.95 (s, H, C=H-H), 9.35 (brs, H, O-H), 12.60 (brs, H, N-H).

$^{13}$C-NMR (75 MHz, DMSO-$d_6$, ppm) δ 111.40, 112.93, 117.83, 119.13, 121.52, 123.58, 125.48, 127.01, 128.35 and 128.41, 128.79 and 128.92, 129.47 and 129.83, 130.30, 132.04, 134.78, 146.10 (C=C-H), 163.89, 167.24, 174.59 (C=O). For C$_{25}$H$_{17}$N$_3$O$_3$S$_2$ calculated: Elemental Analysis: C, 63.68%; H, 3.63%; N, 8.91%; found: C, 63.69%; H, 3.60%; N, 8.93%. HRMS (m/z): [M+H]$^+$ calculated for C$_{25}$H$_{17}$N$_3$O$_3$S$_2$: 472.0784; found: 472.0791.

5-((1H-indol-3-yl)methylene)-2-[(4,5-diphenylthiazol-2-yl)imino]-1,3-thiazolidin-4-one (4d)

m. p. 228°C, $^1$H-NMR (300 MHz, DMSO-$d_6$, ppm) δ 7.20 (d, J=7.47 Hz, H, Ar-H), 7.24-7.26 (m, H, Ar-H), 7.29-7.31 (m, 3H, Ar-H), 7.41 (s, 5H, Ar-H), 7.48 (d, J=1.62 Hz, H, Ar-H), 7.54 (d, J=7.89 Hz, H, Ar-H), 7.61 (d, J=6.78 Hz, H, Ar-H), 7.77 (d, J=2.71 Hz, H, Ar-H), 7.95 (t, J=3.84 Hz, H, Ar-H), 8.03 (s, H, C=H-H), 12.26 (brs, H, N-H), 12.41 (brs, H, N-H). $^{13}$C-NMR (75 MHz, DMSO-$d_6$, ppm) δ 116.60, 117.74, 120.77, 124.26, 125.41, 128.34 and 128.45, 128.77 and 128.83 and 128.88, 129.46 and 129.51, 129.83 and 129.89, 131.93, 132.03, 133.59 (C=C-H), 134.63, 134.78, 146.29 and 146.36, 149.04, 157.27, 162.75, 166.64, 167.61, 174.59 (C=O). For C$_{25}$H$_{17}$N$_3$O$_3$S$_2$ calculated: Elemental Analysis: C, 63.68%; H, 3.63%; N, 8.91%; found: C, 63.69%; H, 3.60%; N, 8.93%. HRMS (m/z): [M+H]$^+$ calculated for C$_{25}$H$_{17}$N$_3$O$_3$S$_2$: 472.0784; found: 472.0791.
Antimicrobial Assay

Design of the antimicrobial activity study was based on comparing minimum inhibitor concentrations (MICs) obtained by the CLSI reference M07–A9 broth microdilution method for antibacterial activity (CLSI, 2012). The antifungal activity test was performed according to EUCAST definitive method EDef 7.1 for Candida species (Rodriguez-Tudela et al., 2008). Four fungi and nine bacteria are on the point of being thirteen strains were investigated by the microdilution method. Sabouraud dextrose agar (SDB) for Candida and Mueller Hinton broth (MHB) for bacteria were used as the feedlot. After overnight incubation, the optical density (OD) values of the developing microorganisms were read at 630 nm for the candidal and at 540 nm for the bacterial strains. Compounds were dissolved in dimethyl sulfoxide (DMSO) were diluted with distilled water and twofold serial dilution method to a concentration from 250 μg/mL to 0.9766 μg/ml for antibacterial activity and a concentration from 250 μg/mL to 15.625 μg/ml for antifungal activity. As a positive control, ketoconazole was used for the fungi and chloramphenicol was used for the bacteria. Also, wells which contain only chemical and only microorganisms were used as negative controls. After 24 hours of incubation, the resorcinol indicator was used as a final concentration of 20 μg/mL for each well. The concentration of the well prior to the colorless or pink-looking well was determined as the MIC. The concentration in the previous well, which appears colorless or pink was determined as the MIC values of the compounds.

Antimicrobial activity was investigated for compounds 4a-4h. Their antimicrobial activities were tested against Candida albicans (ATCC 24433), Candida krusei (ATCC 6258), Candida glabrata (ATCC 90030), Candida parapsilosis (ATCC 22019), Escherichia coli (ATCC 35218), Escherichia coli (ATCC 25922), Yersinia enterocolitica (Y53), Salmonella typhimurium (ATCC 13311), Klebsiella pneumoniae (NCTC 9633), Staphylococcus aureus (ATCC 25923), Bacillus subtilis (NRRL NRS 744), Listeria monocytogenes (ATCC 19111) and Enterococcus faecalis (ATCC 29212).

RESULTS AND DISCUSSION

Chemistry

In this study, we synthesized eight new compounds, which possessed 2-[(4,5-diphenylthiazol-2-yl)imino]-1,3-thiazolidin-4-one moiety as core structure. The synthesis procedure was carried out via four steps. In the first step, 2-bromo-1,2-diphenylethan-1-one was reacted with thiourea for the ring closure. The obtained intermediate (1) was acetylated with chloroacetyl chloride. Then 2-chloro-N-(4,5-diphenylthiazol-2-yl) acetamide (2) and sodium thiocyanate were reacted to gain 2-[(4,5-diphenylthiazol-2-yl)amino]-1,3-thiazolidin-4-one (3). Finally, compound 3 and aryl aldehyde derivatives were reacted for resulting products which were 5-substituted-2-[(4,5-diphenylthiazol-2-yl)imino]-1,3-thiazolidin-4-one derivatives (4a-4h) as shown in Figure 1. All synthesized compounds were fully characterized by analytical and spectral data.
The 1H-NMR spectra of compounds showed signals at δ 7.48-8.03 ppm for methylene (-C=C-H) proton. The broad single peak seen at δ 12.17-12.95 ppm indicated the N-H proton. The appearance of a pair of singlet, doublet, triplet and/or multiplet at δ 6.92-7.95 ppm were due to the aromatic protons. The 13C-NMR spectra of compounds showed signals at δ 108.22-167.61 ppm for aromatic carbon and at δ 166.22-174.61 for carbonyl (C=O) carbon. M+1 peaks in LC-MS/MS spectra were compatible with the calculated molecular weight of the target compounds (4a-4h). Elemental analysis results for C, H, and N elements were admissible with calculated values of the compounds. We also tried to identify isomerism type, but we could not see which isomerism was formed. However, previous studies have shown and proved that the Z isomer is formed in the Knoevenagel reaction if it contains a similar structure core (Abdelazeem, Salama, Maghrabi, 2015; Momose et al., 1991; Vicini et al., 2008). Therefore, our final compounds would show Z isomer with high probability.
ADME Parameters

All findings are shown in Table I with the violations of Lipinski’s rule of five (Lipinski et al., 1997). There’s no discrepancy pursuant to the Lipinski’s rule for some compounds (4c, 4d, 4e and 4f). Even though some compounds (4a, 4b, 4g and 4h) displayed two violations, all compounds showed antimicrobial activity, and they can be formulated to apply for the treatment after future tests.

Results showed that DL scores of 4b and 4c were close to DL scores of standard drugs. However, when the log P values similarity between most active compounds (4b and 4c) and standards was compared, it showed that the synthesized compounds values are higher than that of the standards. Log P may increase the influence intensity, but also it may decrease the solubility degree in solvent for activity tests. Therefore, the dissolution problem might have adversely affected the activity results.

|  | Ar | M. P. (°C) | M. W. | M. F. | Yield (%) | Log P | DL* | V.L. |
|---|---|---|---|---|---|---|---|---|
| 4a | Cl Cl | 295-297 | 508.44 | C_{25}H_{15}Cl_2N_3O_2S_2 | 78 | 8.05 | 0.19 | 2 |
| 4b | -- | 256-258 | 508.44 | C_{25}H_{15}Cl_2N_3O_2S_2 | 80 | 8.05 | 0.33 | 2 |
| 4c | OH OH | 236-238 | 471.55 | C_{25}H_{17}N_3O_2S_2 | 70 | 5.83 | 0.48 | 1 |
| 4d | -- | 227-229 | 478.59 | C_{27}H_{19}N_4OS_2 | 78 | 6.95 | -0.91 | 1 |
| 4e | -- | 223-224 | 442.56 | C_{24}H_{18}N_4OS_2 | 79 | 6.02 | 0.58 | 1 |

(continues on the next page...)
TABLE I - Synthesized compounds (4a-4h) and their some physicochemical parameters

| Ar          | M. P. (°C) | M. W.  | M. F.                  | Yield (%) | Log P | DL* | V.L. |
|-------------|------------|--------|------------------------|-----------|-------|-----|------|
| 4f          | 219-221    | 428.53 | C_{23}H_{16}N_{4}OS_{2} | 79        | 5.95  | -0.66 | 1    |
| 4g          | 119-121    | 507.55 | C_{26}H_{16}FN_{3}OS_{2} | 75        | 7.69  | -0.36 | 2    |
| 4h          | 212-214    | 529.63 | C_{28}H_{23}N_{3}OS_{2} | 78        | 6.63  | 0.30  | 2    |

M.P: Melting Point, M.W: Molecular Weight, M.F: Molecular Formula, c Log P: Octanol/water partition coefficient, D.L: Drug-likeness model score, V.L: Violations of Lipinski Rule. For ketoconazole, its Log P value and D.L. score were stated 3.77 and 1.32, respectively. For chloramphenicol, its Log P value and D.L. score were stated 0.73 and 0.63, respectively. Log P was calculated by www.molinspiration.com/cgi-bin/properties (Accessed: December 22, 2017). DL model score was calculated by http://molsoft.com/mprop/software (Accessed: December 22, 2017)

Antimicrobial Activity

The antimicrobial activity of the compounds 4a-4h was investigated by finding MIC values as shown in TABLE II and III.

TABLE II - Antifungal activity of the compounds 4a-4h as MIC values (µg/mL)

|      | 4a  | 4b  | 4c  | 4d  | 4e  | 4f  | 4g  | 4h  |
|------|-----|-----|-----|-----|-----|-----|-----|-----|
| A    | 125 | 125 | 125 | 62.5*| 125 | 125 | 62.5| 62.5|
| B    | 62.5| 62.5| 62.5| 62.5| 62.5| 62.5| 62.5| 62.5|
| C    | 62.5| 62.5| 62.5| 62.5| 62.5| 31.25*| 62.5| 62.5|
| D    | 125 | 125 | 125 | 125 | 125 | 125 | 62.5*| 62.5*|
| S. D.| <15.625| <15.625| <15.625| <15.625| <15.625| <15.625| <15.625| <15.625|

*: Most active compounds. A: C. albicans (ATCC 24433), B: C. krusei (ATCC 6258), C: C. glabrata (ATCC90030), D: C. parapsilosis (ATCC 22019). S.D: Standard Drug=Ketoconazole.
TABLE III - Antibacterial activity of the compounds 4a-4h as MIC values (µg/mL)

|    | A    | B    | C    | D    | E    | F    | G    | H    | I    |
|----|------|------|------|------|------|------|------|------|------|
| 4a | 125  | 125  | 125  | 125  | 125  | 62.5*| 125  | 125  |      |
| 4b | 62.5*| 62.5 | <31.25*| 62.5*| 62.5*| 62.5*| 62.5*| 62.5*| 62.5*|
| 4c | 125  | <31.25*| 125  | 125  | 125  | 125  | 125  | 62.5*|      |
| 4d | 125  | 125  | 125  | 62.5*| 125  | 125  | 125  | 125  | 125  |
| 4e | 125  | 125  | 125  | 125  | 125  | 125  | 125  | 125  | 125  |
| 4f | 125  | 125  | 125  | 125  | 125  | 125  | 125  | 125  | 125  |
| 4g | 125  | 125  | 125  | 125  | 125  | 125  | 125  | 125  | 125  |
| 4h | 125  | 250  | 62.5 | 62.5*| 62.5*| 62.5*| 62.5*| 125  | 125  |

S. D. 7.8125 7.8125 15.625 15.625 7.8125 7.8125 15.625 7.8125 15.625

*: Most active compounds. A: E. coli (ATCC 35218), B: E. coli (ATCC 25922), C: K. pneumoniae (NCTC 9633), D: Y. enterocolitica (Y53), E: S. typhimurium (ATCC 13311), F: S. aureus (ATCC 25923), G: L. monocytogenes (ATCC 19111), H: B. subtilis (NRRL NRS 744), I: E. faecalis (ATCC 29212). A-E: Gram negative bacteria, F-I: Gram positive bacteria. S.D: Standard Drug=Chloramphenicol.

All compounds displayed antifungal activity. Especially, compound 4f exhibited more efficacy than other compounds against C. glabrata (MIC: 31.25 µg/ml). Also, 4d, 4g and 4h demonstrated antifungal activity against C. albicans (ATCC 24433) at the same concentration (MIC: 62.5 µg/ml). In general, the most active compounds 4g and 4h were indicated antifungal activity against all Candida species at the same concentration (MIC: 62.5 µg/ml). The other compounds (4a, 4b, 4c, 4d, 4e and 4f) revealed antifungal activity against C. albicans (ATCC 24433) and C. parapsilopsis (ATCC22019) at the same concentration (MIC: 125.0 µg/ml). Once more the compounds 4a, 4b, 4c, 4d and 4e showed antifungal activity against C. krusei (ATCC 6258), C. glabrata (ATCC90030) at the same concentration (MIC: 62.5 µg/ml).

In antifungal activity investigation, we stated 4f as the most active compound. It was thought that it can be caused by (1H-pyrrol-2-yl) methylene substitution on fifth position of thiazolidinone. This can be explained by its low molecular weight, and another factor it can be explained by nucleus of (2-substituted)-1H-pyrrole which proved their antifungal activity (Bhardwaj et al., 2015).

Also, all compounds exhibited antibacterial activity. Generally, compound 4b (MIC: 62.5 µg/ml) was the most active compound against all bacterial species. Particularly, compound 4b (MIC: <31.25 µg/ml) was determined as the most active compound against K. pneumoniae (NCTC 9633), and compound 4c (MIC: <31.25 µg/ml) was stated as the most active compound against E. coli (ATCC 25922). Extraordinarily, compound 4b (MIC: 62.5 µg/ml) was two times more active against E. coli (ATCC 35218) and B. subtilis (NRRL NRS 744). Compounds 4b, 4d and 4h (MICs: 62.5 µg/ml) were more active against Y. enterocolitica (Y53) than the other compounds. Similarly, compounds 4b and 4h (MIC: 62.5 µg/ml) were more active against S. typhimurium (ATCC 13311) and S. aureus (ATCC 25923). Also, compounds 4a, 4b and 4h (MICs: 62.5 µg/ml) were found more effective against L. monocytogenes (ATCC 19111). Likewise, 4b and 4c (MIC: 62.5 µg/ml) were stated more effective against E. faecalis (ATCC 29212).

Generally, all compounds showed antibacterial activity and it could be explained by small groups such as oxo substitution at fourth position of thiazole-4(5H)-one. Particularly, these results showed that...
2,6-dichlorobenzylidene (compound 4b) at 5-position of thiazole-4(5H)-one increased the antibacterial activity. One of the reasons for this could be compounds' log P values which explain high solubility in organic phase (Lipinski et al., 1997). Another reason could be the effect of fifth position substitution of thiazole nucleus on previous study (Bondock, Naser, Ammar, 2013). As known, the types of substitutions and their positions on benzene ring are important. Here it was observed that the presence of electron withdrawing group such as chloride at ortho and meta positions of the benzene ring caused an increased antibacterial activity. These reasons could clarify why compound 4b was more active than the other compounds.

**Foreseen Toxicity Risks**

Hepatotoxicity, immunotoxicity, mutagenicity and cytotoxicity risks belonging to synthesized molecules and standard drugs were estimated and displayed in Table IV. According to the findings, compound 4h may display immunotoxicity like ketoconazole. Already it is a characteristic property of antifungal drugs. Also, all final compounds may cause hepatotoxicity despite not as much as ketoconazole. But, compounds 4a, 4b and 4e might show low cytotoxicity in comparison to standard drugs. On the other hand, final compounds are predicted to have no mutagenic influences.

In summary, we synthesized novel 5-substituted-2-[(4,5-diphenylthiazol-2-yl)imino]-1,3-thiazolidin-4-one derivatives (4a-4h) and evaluated their antimicrobial activity against four fungi and nine bacterial species in this study. In general, all compounds (4a-4h) showed antimicrobial activity against all fungi and bacterial species. Compounds 4g and 4h were the most active compounds against *Candida* species. Compound 4b takes intensively an eager interest to *K. pneumoniae* (NCTC 9633) even though it displayed equal effect against other bacterial species. Also, compound 4e was the most active compound against *E. coli* (ATCC 25922).

**TABLE IV** - Predicted toxicity risks of the compounds

|     | A     | B     | C     | D     |     | A     | B     | C     | D     |
|-----|-------|-------|-------|-------|-----|-------|-------|-------|-------|
| 4a  | + (62) | - (91) | - (57) | - (79) | 4e  | + (58) | - (98) | - (53) | - (86) |
| 4b  | + (62) | - (94) | - (57) | - (79) | 4f  | + (63) | - (95) | - (54) | - (75) |
| 4c  | + (66) | - (63) | - (58) | - (65) | 4g  | + (69) | - (91) | - (58) | - (75) |
| 4d  | + (50) | - (98) | - (52) | - (63) | 4h  | + (58) | + (68) | - (53) | - (62) |
| SD-1| + (76) | + (98) | - (69) | - (63) | SD-2| - (70) | - (99) | + (63) | - (64) |

A: Hepatotoxicity, B: Immunotoxicity, C: Mutagenicity, D: Cytotoxicity, SD-1: Ketoconazole and SD-2: Chloramphenicol. +: Active, -: Inactive. Probability value of active or inactive was displayed as percentage in parentheses. It was calculated by http://tox.charite.de/protox_II (Accessed: September 3, 2019)

**CONFLICT OF INTEREST**

Authors have no conflict of interest regarding this study.

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