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Synthesis and Antimicrobial Evaluation of New 3-Alkyl/aryl-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinones

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New 4-thiazolidinone derivatives of benzilic acid (α,α-diphenyl-α-hydroxyacetic acid) have been synthesized and evaluated for antibacterial and antifungal activities. The reaction of 1-(α,α-diphenyl-α-hydroxy)acetyl-4-alkyl/arylthiosemicarbazides with ethyl 2-bromopropionate gave 3-alkyl/aryl-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinone derivatives. Their antibacterial and antifungal activities were evaluated against *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853, *E. coli* ATCC 25922, *C. albicans* ATCC 10231, *C. parapsilosis* ATCC 22019, *C. krusei* ATCC 6258, *T. mentagrophytes var. erinacei* NCPF 375, *M. gypseum* NCPF 580 and *T. tonsurans* NCPF 245. **3e**, **3f**, **3g** and **3h** showed the highest antibacterial activity. Particularly **3a** and **3e** showed the highest antifungal activities against *C. parapsilosis* ATCC 22019, *T. tonsurans* NCPF 245 and *M. gypseum* NCPF 580.

Key words: Benzilic acid, 4-Thiazolidinone, Antibacterial activity, Antifungal activity

INTRODUCTION

The extensive use of antibiotics has led to the appearance of multi-drug resistant microbial pathogens (Frère, 1995). This highlights the incessant need for the development of new classes of antimicrobial agents and alteration of known drugs in such way that would allow them to retain their physiological action, but reducing their resistance to the pathogen. The design of novel chemotherapeutic agents is particularly beneficial due to their dissimilar mode of action which can avoid cross resistance to known drugs.

There has been considerable interest in the chemistry of 4-thiazolidinone ring systems, which is a core structure in various synthetic pharmaceuticals displaying a broad spectrum of biological activities (Vigorita et al., 2001; Kavitha et al., 2006). 4-Thiazolidinone derivatives are known to exhibit diverse bioactivities such as antibacterial (Mishra et al., 2007; Aquino et al., 2008; Bondock et al., 2007; Shah et al., 2007; Kumar et al., 2006; Rida et al., 2005), antifungal (Özkirimli et al., 2008; Kaplancikli et al., 2008; Siddiqui et al., 2003), antituberculosis (Küçükgüzel et al., 2002; Küçükgüzel et al., 2006; Karali et al., 2007), anti-HIV (Rawal et al., 2008; Balzarini et al., 2007; Rao et al., 2004; Rao et al., 2004; Rao et al., 2003), anticancer (Ali et al., 2007), anticonvulsant (Archana et al., 2002; Amin et al., 2008; Gürsoy et al., 2005), anti-inflammatory (Kumar et al., 2009; Bhati et al., 2008; Goel et al., 1999) and antihistaminic (Diurno et al., 1999) activities. On the other hand, α,α-diphenyl-α-hydroxy)acetyl moiety are also associated with various biological properties including antimicrobial activity (Ilhan and Ergenç, 1992; Ilhan et al., 1994). As a continuation of our previous studies on 4-thiazolidinone derivatives (Ulusoy et al., 2002; Çapan et al., 1999; Ulusoy et al., 1998; Ulusoy et al., 1997; Ulusoy et al., 1996; Çapan et al., 1996) and on α,α-diphenyl-α-hydroxy)acetyl moiety (Ilhan et al., 1996), we synthesized new 3-alkyl/aryl-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinones in order to screen them for antibacterial and antifungal activities. Structural elucidation of these compounds was

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performed by IR, ^{1}H-NMR, mass spectroscopy and elemental analysis.

MATERIALS AND METHODS

Melting points were estimated with a Büchi 530 capillary melting point apparatus in open capillary tubes and are uncorrected. IR spectra were recorded (in KBr) on a Perkin Elmer 1600 FT Infrared spectrophotometer. ^{1}H-NMR spectra were recorded on Bruker AC 200 (200 MHz) spectrophotometer and Bruker DPX 400 (400 MHz) spectrophotometer using tetramethylsilane as internal standard. EI/MS were recorded on a VG Zab Spec (70 eV) mass spectrometer. Elemental analyses were performed on a Carlo Erba 1106 elemental analyzer. All chemicals were obtained from Merck.

General procedure for the synthesis of compounds (3a-j)

To a suspension of 1-(α,α-diphenyl-α-hydroxy)acetyl-4-alkyl/arylthiosemicarbazides **2** (0.05 mol) in absolute ethanol (25 ml) were added anhydrous sodium acetate (0.2 mol) and ethyl 2-bromopropionate (0.05 mol). The reaction mixture was refluxed for 5 h, cooled, diluted with water and allowed to stand overnight. The crystals were filtered, dried and purified by crystallization from ethanol or ethanol/water.

3-Ethyl-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinone (3a)
Yield 78%; m.p. 168-169°C; IR (KBr): ν (cm^{-1}) 3625 (OH), 3217 (NH), 1715, 1659 (C=O); ^{1}H-NMR (200 MHz, DMSO-d_6): δ (ppm) 1.13 (3H, t, J = 7.0 Hz, N-CH_2-C**H**$_3$); 1.51 (3H, d, J = 7.1 Hz, thiazolidinone C_5-CH_3); 3.68 (2H, q, J = 7.0 Hz, N-CH_2); 4.35 (1H, q, J = 7.1 Hz, thiazolidinone C_5-H); 6.88-7.54 (11H, m, Ar-H and OH); 9.91 (1H, s, NH); EIMS (70 eV) m/z (%): 383 (M^+, 0.4), 365 (45), 336 (29), 208 (20), 201 (11), 183 (94), 173 (34), 165 (36), 158 (32), 130 (8), 105 (100, base peak), 77 (42). *Anal.* Calcd for $C_{20}H_{21}N_3O_3S$: C, 62.64; H, 5.52; N, 10.95. Found: C, 62.45; H, 5.76; N, 10.53.

3-Butyl-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinone (3b)
Yield 98%; m.p. 131-132°C; IR (KBr): ν (cm^{-1}) 3628 (OH), 3309 (NH), 1713, 1673 (C=O); ^{1}H-NMR (200 MHz, DMSO-d_6): δ (ppm) 0.86 (3H, t, J = 7.2 Hz, N-CH_2-CH_2-CH_2-C**H**$_3$); 1.22-1.26 (2H, m, N-CH_2-CH_2-C**H**$_2$-CH_3); 1.48-1.55 (5H, m, N-CH_2-C**H**$_2$ and thiazolidinone C_5-CH_3); 3.63 (2H, t, J = 7.0 Hz, N-CH_2); 4.37 (1H, q, J = 7.1 Hz, thiazolidinone C_5-H); 6.92 (1H, s, OH), 7.28-7.41 (10H, m, Ar-H); 10.10 (1H, s, NH); EIMS (70 eV) m/z (%): 411 (M^+, 4), 393 (98), 364 (37), 228 (16), 208 (37), 201 (42), 183 (100, base peak), 165 (34), 131 (22), 105 (47), 77 (14). *Anal.* Calcd for $C_{22}H_{25}N_3O_3S$: C, 64.21; H, 6.12; N, 10.21. Found: C, 64.12; H, 6.37; N, 9.56.

3-(2-Phenylethyl)-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinone (3c)
Yield 93%; m.p. 155-156°C; IR (KBr): ν (cm^{-1}) 3500 (OH), 3383 (NH), 1721, 1650 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 1.51 (3H, d, J = 7.1 Hz, thiazolidinone C_5-CH_3); 2.64-3.12 (2H, m, C**H**$_2$-C_6H_5); 3.98-4.07 (2H, m, N-CH_2); 4.39 (1H, q, J = 7.1 Hz, thiazolidinone C_5-H); 7.00 (1H, s, OH); 7.31-7.60 (15H, m, Ar-H), 10.20 (1H, s, NH); EIMS (70 eV) m/z (%): 459 (M^+, 12), 442 (8), 277 (5), 249 (70), 234 (83), 105 (100, base peak), 104 (71), 77 (44). *Anal.* Calcd for $C_{26}H_{25}N_3O_3S$: C, 67.95; H, 5.48; N, 9.14. Found: C, 67.53; H, 5.64; N, 9.10.

3-Benzyl-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinone (3d)
Yield 88%; m.p. 152-153°C; IR (KBr): ν (cm^{-1}) 3626 (OH), 3311 (NH), 1723, 1674 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 1.68 (3H, d, J = 7.1 Hz, thiazolidinone C_5-CH_3); 4.62 (1H, q, J = 7.1 Hz, thiazolidinone C_5-H); 5.00 (2H, s, N-CH_2); 7.00 (1H, s, OH); 7.41-7.58 (15H, m, Ar-H), 10.20 (1H, s, NH); EIMS (70 eV) m/z (%): 445 (M^+, observed with increased intensity), 408 (5), 263 (83), 262 (90), 235 (8), 220 (5), 183 (35), 105 (93), 91 (100, base peak), 77 (68). *Anal.* Calcd for $C_{25}H_{23}N_3O_3S$: C, 67.39; H, 5.20; N, 9.43. Found: C, 67.26; H, 4.99; N, 9.42.

3-Phenyl-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinone (3e)
Yield 95%; m.p. 200-201°C; IR (KBr): ν (cm^{-1}) 3464 (OH), 3279 (NH), 1725, 1656 (C=O); ^{1}H-NMR (200 MHz, DMSO-d_6): δ (ppm) 1.63 (3H, d, J = 7.1 Hz, thiazolidinone C_5-CH_3); 4.53 (1H, q, J = 7.1 Hz, thiazolidinone C_5-H); 6.92 (1H, s, OH); 7.23-7.52 (15H, m, Ar-H), 9.96 (1H, s, NH); EIMS (70 eV) m/z (%): 431 (M^+, 0.4), 413 (44), 249 (38), 221 (87), 208 (16), 205 (63), 183 (80), 165 (37), 105 (100, base peak), 77 (59). *Anal.* Calcd for $C_{24}H_{21}N_3O_3S$: C, 66.80; H, 4.90; N, 9.73. Found: C, 67.00; H, 5.27; N, 9.62.

3-(4-Bromophenyl)-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinone (3f)
Yield 98%; m.p. 204-205°C; IR (KBr): ν (cm^{-1}) 3629 (OH), 3315 (NH), 1761, 1700 (C=O); ^{1}H-NMR (200 MHz, DMSO-d_6): δ (ppm) 1.53 (3H, d, J = 7.1 Hz, thiazoli-

dinone C_5-CH_3); 4.46 (1H, q, J = 7.0 Hz, thiazolidinone C_5-H); 6.82 (2H, d, J = 8.5 Hz, Ar-H); 6.95 (1H, s, OH); 7.30-7.67 (12H, m, Ar-H), 10.87 (1H, s, NH); EIMS (70 eV) *m/z* (%): 509, 511 (M^+, $(M+2)^+$, 13, 14), 491, 493 (5, 6), 326, 328 (16, 16), 299, 301 (20, 21), 284, 286 (56, 57), 223, 225 (5, 5), 196, 198 (18, 17), 183 (86), 105 (100, base peak), 77 (37). *Anal.* Calcd for $C_{24}H_{20}BrN_3O_3S$: C, 56.47; H, 3.94; N, 8.23. Found: C, 56.75; H, 4.19; N, 7.92.

3-(4-Chlorophenyl)-2-[((α,α-diphenyl-α-hydroxy) acetyl)hydrazono]-5-methyl-4-thiazolidinone (3g) Yield 96%; m.p. 214-215°C; IR (KBr): ν (cm^{-1}) 3625 (OH), 3421 (NH), 1764, 1724 (C=O); ^{1}H-NMR (200 MHz, DMSO-d_6): δ (ppm) 1.53 (3H, d, J = 6.3 Hz, thiazolidinone C_5-CH_3); 4.47 (1H, q, J = 7.1 Hz, thiazolidinone C_5-H); 6.88 (2H, d, J = 8.5 Hz, Ar-H); 7.01 (1H, s, OH); 7.30-7.54 (12H, m, Ar-H), 10.98 (1H, s, NH); EIMS (70 eV) *m/z* (%): 465, 467 (M^+, $(M+2)^+$, 0.7, 0.2), 282 (9), 240, 242 (20, 7), 208 (7), 182 (69), 105 (100, base peak), 78 (58), 63 (60). *Anal.* Calcd for $C_{24}H_{20}ClN_3O_3S$: C, 61.86; H, 4.32; N, 9.01. Found: C, 61.56; H, 4.71; N, 8.99.

3-(4-Fluorophenyl)-2-[((α,α-diphenyl-α-hydroxy) acetyl)hydrazono]-5-methyl-4-thiazolidinone (3h) Yield 89%; m.p. 197-198°C; IR (KBr): ν (cm^{-1}) 3563 (OH), 3360 (NH), 1754, 1715 (C=O); ^{1}H-NMR (200 MHz, DMSO-d_6): δ (ppm) 1.68 (3H, d, J = 6.9 Hz, thiazolidinone C_5-CH_3); 4.59 (1H, q, J = 7.0 Hz, thiazolidinone C_5-H); 7.03, 7.04 (2H, dd, J = 8.6, 8.7 Hz, Ar-H); 7.09 (1H, s, OH); 7.32-7.64 (12H, m, Ar-H), 11.00 (1H, s, NH); EIMS (70 eV) *m/z* (%): 449 (M^+, 0.4), 266 (5), 239 (8), 224 (24), 183 (23), 165 (11), 153 (9), 113 (9), 105 (100, base peak), 95 (13), 77 (65), 59 (19). *Anal.* Calcd for $C_{24}H_{20}FN_3O_3S$: C, 64.12; H, 4.48; N, 9.34. Found: C, 63.99; H, 4.08; N, 9.28.

3-(4-Methylphenyl)-2-[((α,α-diphenyl-α-hydroxy) acetyl)hydrazono]-5-methyl-4-thiazolidinone (3i) Yield 92%; m.p. 174-175°C; IR (KBr): ν (cm^{-1}) 3478 (OH), 3321 (NH), 1727, 1679 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 1.72 (3H, d, J = 7.0 Hz, thiazolidinone C_5-CH_3); 2.49 (3H, s, Ar-CH_3), 4.61 (1H, q, J = 7.1 Hz, thiazolidinone C_5-H); 6.94 (2H, d, J = 8.1 Hz, Ar-H); 7.09 (1H, s, OH); 7.32-7.66 (12H, m, Ar-H), 11.00 (1H, s, NH); EIMS (70 eV) *m/z* (%): 445 (M^+, observed with increased intensity), 262 (27), 235 (33), 234 (52), 220 (90), 219 (45), 183 (16), 165 (7), 131 (7), 105 (100, base peak), 91 (22), 77 (93), 58 (49). *Anal.* Calcd for $C_{25}H_{23}N_3O_3S$: C, 67.39; H, 5.20; N, 9.43. Found: C, 67.07; H, 5.42; N, 9.32.

3-(4-Nitrophenyl)-2-[((α,α-diphenyl-α-hydroxy) acetyl)hydrazono]-5-methyl-4-thiazolidinone (3j) Yield 66%; m.p. 206-207°C; IR (KBr): ν (cm^{-1}) 3626 (OH), 3353 (NH), 1756, 1719 (C=O); ^{1}H-NMR (400 MHz, DMSO-d_6): δ (ppm) 1.71 (3H, d, J = 6.5 Hz, thiazolidinone C_5-CH_3); 4.68 (1H, q, J = 7.1 Hz, thiazolidinone C_5-H); 7.15 (1H, s, OH); 7.22-7.64 (12H, m, Ar-H), 8.41 (2H, d, J = 8.9 Hz, Ar-H); 11.10 (1H, s, NH); EIMS (70 eV) *m/z* (%): 183 (10), 165 (6), 152 (4), 105 (70), 82 (9), 77 (100, base peak), 60 (41), 50 (26). *Anal.* Calcd for $C_{24}H_{20}N_4O_5S$: C, 60.49; H, 4.23; N, 11.75. Found: C, 60.22; H, 4.28; N, 11.66.

Antimicrobial activity

All compounds to be tested were dissolved in DMSO at a stock concentration of 3200 μg/mL. The final desired concentration were prepared with RPMI 1640 medium for *Candida* species and dermatophytes and with Mueller-Hinton broth of bacteria. The final DMSO concentration was reduced to 1%.

Antibacterial activity

MICs were determined by the microbroth dilution method using the National Committee for Clinical Laboratory Standards (NCCLS) recommendations (Clinical and Laboratory Standards Institute, 2005). Mueller-Hinton broth (Oxoid) was used as the test medium. An inoculum of approximately 5×10^5 CFU · cm^{-3} was delivered per well. Serial twofold dilutions of the test compounds (64-0.25 μg/mL) and extra dilutions (0.12-0.015 μg/mL) for antibiotic standards were prepared. Plates were incubated for 16-20 h at 35°C in an ambient air incubator. The lowest concentration of the test compounds inhibiting visible growth was taken as the MIC value.

Antifungal activity for Candida species

MICs were determined by the microbroth dilution method using the NCCLS (National Committee for Clinical Laboratory) Standards recommendations (Reference method for broth dilution antifungal susceptibility testing of yeast, 2002). RPMI broth was prepared from RPMI 1640 medium (Sigma) supplemented with 0.3 g of glutamine per liter, bufferred with 3-(N-morpholino)-propanesulfonic acid (MOPS), and adjusted to pH 7.0. A working suspension of the inoculum was prepared by a 1:100 dilution of the 0.5 McFarland standards yeast suspension in 0.85% saline followed by a 1:20 dilution in RPMI broth.

Two-fold dilutions of test compounds from 64 to 0.25 μg/mL were prepared with the working suspension of the inoculum. Extra dilutions (0.12-0.015 mg/mL) were added for itraconazole. The plates were incubat-

ed at 35°C for 48 h in ambient air. The MIC is the lowest concentration of a compound that inhibits growth of the organism as detected visually.

Antifungal activity for dermatophytes

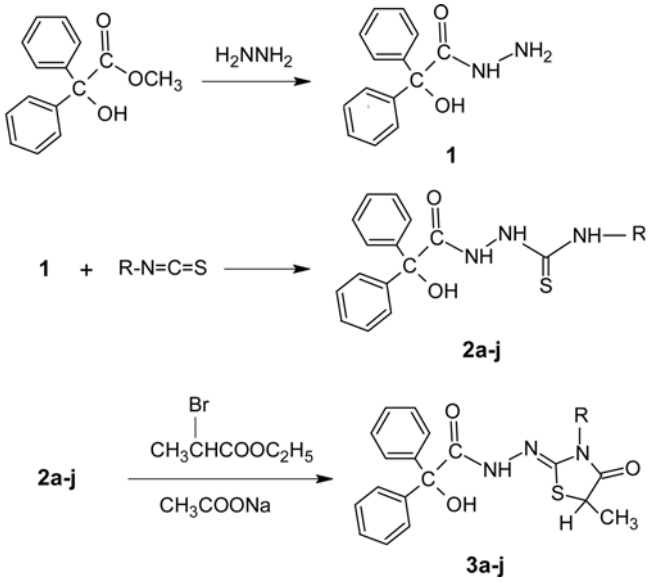
Microdilution method was used according to a standard protocol by NCCLS (Clinical and Laboratory Standards Institute, 2005). RPMI 1640 broth with L-glutamine without sodium bicarbonate was used and buffered with 3-(N-morpholino)propanesulfonic acid (MOPS). The medium was adjusted to pH 7.0 at 25°C. Preparation of inoculum suspensions of dermatophytes were based according to the NCCLS guidelines (National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing filamentous fungi, 2002) and previously described procedure (Fernandez-Torres et al., 2002).

The isolates were subcultured on to potato dextrose agar plates at 28°C, during 7-14 days. The fungal colonies were covered with 1 mL of sterile 0.85% saline, and suspensions were made by gently probing the surface with the tip of Pasteur pipette. The resulting mixture of conidia and hyphal fragments was withdrawn and transferred to a sterile tube. Heavy particles were allowed to settle for 15-20 min at room temperature; the upper suspension was mixed with a vortex for 15 sec. The turbidity of supernatants was measured spectrophotometrically at a wavelength of 530 nm, and transmission was adjusted to 65 to 75%. These stock suspensions were diluted 1:50 in RPMI medium to obtain the final inoculum sizes, which range from 0.4×10^4 to 5×10^4 CFU/mL. Microdilution plates were prepared and frozen at -70°C until needed. Rows from 2 to 12 contained the series of drug dilutions in 100 μL volumes and first row contained 100 μL of drug-free medium, which served as the growth control. Each well was inoculated on the day of the test with 100 μL of the corresponding inoculum. This step brought the drug dilutions and inoculum size to the final test concentrations given above. The microplates of dermatophytes were incubated at 28°C during 7 days. The microplates were read visually with the aid to an inverted reading mirror after 7 days for dermatophytes. For all drugs, the MIC was defined as the lowest concentration showing 100% inhibition of growth.

RESULTS AND DISCUSSION

Chemistry

The target compounds were prepared from methyl benzilate (α,α-diphenyl-α-hydroxyacetic acid methyl ester) by a three step synthesis as shown in Scheme 1.



Scheme 1. Synthesis of compounds **3a-j**

By heating methyl benzilate and hydrazine-hydrate in ethanol, α,α-diphenyl-α-hydroxyacetic acid hydrazide **1** was obtained.

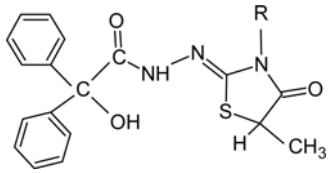
Hydrazide and alkyl/aryl isothiocyanates were heated in ethanol to yield 1-(α,α-diphenyl-α-hydroxy)acetyl-4-alkyl/arylthiosemicarbazides **2a-j** (Ergenç et al., 1992). The thiosemicarbazides were then reacted with ethyl 2-bromopropionate in the presence of anhydrous sodium acetate in absolute ethanol to yield 3-alkyl/aryl-2-[((α,α-diphenyl-α-hydroxy)acetyl)hydrazono]-5-methyl-4-thiazolidinones **3a-j**. (Table I). The structures of the obtained compounds were elucidated by spectral data.

In the IR spectra, some significant stretching bands due to O-H, N-H and C=O were observed at 3629-3464 cm^{-1}, 3421-3217 cm^{-1} and 1724-1650 cm^{-1}, respectively. A new strong band at 1764-1713 cm^{-1} in the spectra of **3a-j** provided firm support for ring closure (Cesur et al., 1994). In the ^{1}H-NMR spectra of compounds **3a-j**, NH protons appeared as a singlet (1H) at 11.10-9.91 ppm, the C**H**-CH_3 protons appeared as a quartet (1H) at 4.68-4.35 ppm and CH-C**H**$_3$ protons appeared as a doublet (3H) at 1.72-1.48 ppm which proved the closure of 4-thiazolidinone ring (Farghaly et al., 1990). In the EI-MS spectra of the compounds except **3j**, the molecular ion peaks which appeared in different intensities, also proved the structures. The fragmentation route of all compounds were in accordance with the literature (De Lima et al., 2002).

Antimicrobial activity

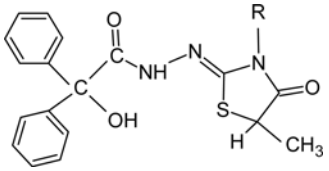
All of the compounds were evaluated for *in vitro* antibacterial and antifungal activity against repre-

Table I. Physicochemical data of compounds (**3a-j**)



Compound	R	Molecular formula (MW)	Mp (°C)	Yield (%)	Analysis (calc./found)		
					C	H	N
3a	C_2H_5	$C_{20}H_{21}N_3O_3S$	168-169	78	62.64	5.52	10.95
		(383.47)			62.45	5.76	10.53
3b	C_4H_9	$C_{22}H_{25}N_3O_3S$	131-132	98	64.21	6.12	10.21
		(411.52)			64.12	6.37	9.56
3c	$CH_2CH_2C_6H_5$	$C_{26}H_{25}N_3O_3S$	155-156	93	67.95	5.48	9.14
		(459.57)			67.53	5.64	9.10
3d	$CH_2C_6H_5$	$C_{25}H_{23}N_3O_3S$	152-153	88	67.39	5.20	9.43
		(445.54)			67.26	4.99	9.42
3e	C_6H_5	$C_{24}H_{21}N_3O_3S$	200-201	95	66.80	4.90	9.73
		(431.51)			67.00	5.27	9.62
3f	$C_6H_4Br(4)$	$C_{24}H_{20}BrN_3O_3S$	204-205	98	56.47	3.94	8.23
		(510.41)			56.75	4.19	7.92
3g	$C_6H_4Cl(4)$	$C_{24}H_{20}ClN_3O_3S$	214-215	96	61.86	4.32	9.01
		(465.95)			61.56	4.71	8.99
3h	$C_6H_4F(4)$	$C_{24}H_{20}FN_3O_3S$	197-198	89	64.12	4.48	9.34
		(449.50)			63.99	4.08	9.28
3i	$C_6H_4CH_3(4)$	$C_{25}H_{23}N_3O_3S$	174-175	92	67.39	5.20	9.43
		(445.54)			67.07	5.42	9.32
3j	$C_6H_4NO_2(4)$	$C_{24}H_{20}N_4O_5S$	206-207	66	60.49	4.23	11.75
		(476.51)			60.22	4.28	11.66

Table II. Antibacterial activity of synthesized compounds (**3a-j**) (MIC μg/mL)



Compound/ *microorg.	R	A	B	C
3a	C_2H_5	>64	>64	64
3b	C_4H_9	>64	>64	>64
3c	$CH_2CH_2C_6H_5$	64	>64	64
3d	$CH_2C_6H_5$	64	>64	>64
3e	C_6H_5	32	32	32
3f	$C_6H_4Br(4)$	32	64	32
3g	$C_6H_4Cl(4)$	32	>64	32
3h	$C_6H_4F(4)$	64	32	32
3i	$C_6H_4CH_3(4)$	64	>64	64
3j	$C_6H_4NO_2(4)$	>64	>64	>64
Levofloxacin		0.12	0.5	0.015

*****A=*S. aureus* ATCC 29213, B=*P. aeruginosa* ATCC 27853, C=*E. coli* ATCC 25922.

sentative bacteria: *S. aureus* ATCC 29213, *P. aeruginosa* ATCC 27853 and *E. coli* ATCC 25922 and fungi: *C. albicans* ATCC 10231, *C. parapsilosis* ATCC 22019, *C. krusei* ATCC 6258, *T. mentagrophytes var. erinacei* NCPF 375, *M. gypseum* NCPF 580 and *T. tonsurans* NCPF 245 using the microbroth dilution method (Clinical and Laboratory Standards Institute, 2005; National Committee for Clinical Laboratory Standards. Reference method for broth dilution antifungal susceptibility testing of yeasts, 2002). As can be seen in Table II, **3e** (R=C_6H_5), **3f** (R= 4-BrC_6H_4), **3g** (R= 4-ClC_6H_4), and **3h** (R= 4-FC_6H_4) showed the highest antibacterial activity. Particularly R= C_2H_5 and R=C_6H_5 substituted derivatives **3a** and **3e** showed the highest antifungal activities against *C. parapsilosis* ATCC 22019 (**3a** and **3e**; MIC=16 μg/mL), *T. tonsurans* NCPF 245 (**3a** and **3e**; MIC=16 μg/mL) and *M. gypseum* NCPF 580 (**3e**; MIC=16 μg/mL) (Table III).

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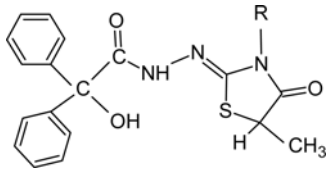
Table III. Antifungal activity of synthesized compounds (**3a-j**) (MIC μg/mL)



Compound/ *microorg.	R	A	B	C	D	E	F
3a	C_2H_5	32	16	32	32	32	16
3b	C_4H_9	64	64	64	64	32	32
3c	$CH_2CH_2C_6H_5$	64	32	64	>64	64	64
3d	$CH_2C_6H_5$	>64	32	>64	64	32	64
3e	C_6H_5	32	16	32	32	16	16
3f	$C_6H_4Br(4)$	32	64	64	64	64	64
3g	$C_6H_4Cl(4)$	64	32	32	64	64	32
3h	$C_6H_4F(4)$	64	32	32	32	32	32
3i	$C_6H_4CH_3(4)$	32	64	64	64	64	32
3j	$C_6H_4NO_2(4)$	64	>64	>64	>64	>64	>64
Itraconazole		0.12	0.06	0.12	n.t.	n.t.	n.t.
Amphotericin B		n.t.	n.t.	n.t.	0.5	0.5	0.25

*A=*C. albicans* ATCC 10231, B=*C. parapsilosis* ATCC 22019, C=*C. krusei* ATCC 6258, D=*T. mentagrophytes var. erinacei* NCPF 375, E=*M. gypseum* NCPF 580, F=*T. tonsurans* NCPF 245, n.t.=not tested.

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