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Synthesis and Antimicrobial Activity of Some New 3-Substituted Benzyl-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene)-thiazolidine-2,4-dione Derivatives

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A new series of thiazolyl thiazolidine-2,4-dione (**Va-f**) were synthesized and their structures were elucidated by IR, ^{1}H-NMR, mass spectra and elementary analysis. The synthesized compounds were tested for their antimicrobial activities against *Candida albicans*, *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli*. Compounds **Va-b, Vd-f** showed high activity against *Escherichia coli* comparable to ampicillin.

Key Words: Thiazolidine-2,4-diones, thiazole derivatives, antimicrobial activities.

Introduction

The presence of a thiazolidine ring in penicillins and related derivatives was the first recognition of its occurrence in nature [1]. Thiazolidine derivatives are reported to show a variety of biological activities. Depending on the substituents, this heterocycle can induce different pharmacological properties such as antibacterial, antifungal[2], antidiabetic[3,4], cardiotonic[5], anticonvulsant[6], cyclooxygenase and lipoxygenase inhibitory[7]. Thiazoles and their derivatives have been reported to possess antibacterial[8], and antifungal[9] activities. It has been established that the introduction of arylidene moieties at different positions of the thiazolidine ring enhanced antimicrobial activity[2,10]. In the present study, in view of the antimicrobial property of the above pharmacophores, some novel thiazole derivatives that contain thiazolidinedione moiety were synthesized.

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Experimental

Melting points were determined with a Büchi SMP-20 melting point apparatus and were uncorrected. All instrumental analyses were performed in the Central Laboratory of the Pharmacy Faculty of Ankara University. IR spectra were recorded on a Jasco FT/IR-420 spectrometer as potassium bromide disks. ^{1}H NMR spectra were measured with a VARIAN Mercury 400 FT-NMR spectrometer in $CDCl_3$ and DMSO-d_6. All chemical shifts were reported as δ (ppm) values. Mass spectra were recorded on VG Waters Micromass ZQ by the ESI (+) method. Elementary analyses were performed on a Leco CHNS 932 analyzer and satisfactory results ±0.4% of calculated values (C, H, N) were obtained. For the chromatographic analysis Merck Silica Gel 60 (230-400 mesh ASTM) was used. The chemical reagents used in the synthesis were purchased from E. Merck (Darmstadt, Germany) and Aldrich (Milwaukee, MI, USA). 2,4-TZD (**I**)[2], 2,4-dichlorothiazole-5-carbaldehyde (**II**)[11], 4-chloro-2-piperidin-1yl-thiazole-5-carbaldehyde (**III**)[12] and substituted-2,4-TZD (**IVa-f**)[2,13,14] were synthesized according to the literature.

General procedure for the synthesis of compounds Va-f

Synthesis of 2,4-dichlorothiazole-5-carbaldehyde (II)

2,4-Dichlorothiazole-5-carbaldehyde (**II**) was prepared with N,N-Dimethylformamide (0.021 mol) and a suspension of 2,4-TZD (**I**) (0.021 mol) in phosphoryl chloride (0.129 mol), m.p.: 48 °C (Ref. 11 m.p.: 48-49 °C).

Synthesis of 4-chloro-2-piperidin-1yl-thiazole-5-carbaldehyde (III)

To a stirred suspension of 2,4-dichlorothiazole-5-carbaldehyde **(II)** (0.001 mol) and potassium carbonate (0.001 mol) in acetonitrile (5 mL) was added piperidine (0.001 mol), followed by stirring for 3 h at room temperature. The product was purified by column chromatography silica gel 60 (230-400 mesh ASTM) using hexane:dichloromethane (1:1) as eluent, m.p.: 88 °C (Ref. 12 m.p.: 88-90 °C).

Synthesis of compounds IVa-f

A mixture of 2,4-TZD (**I**) (2.34 g, 0.02 mol), substituted benzyl halide (0.02 mol) and sodium hydroxide (0.8 g, 0.02 mol) in 20 mL of 50% ethanol was refluxed for 18 h. The crude product was crystallized from ethanol. [**IVa** m.p.: 62-63 °C (Ref. 12 m.p.: 61 °C), **IVb** m.p.: 83 °C (Ref. 2 m.p.: 82 °C), **IVc** m.p.: 96 °C (Ref. 13 m.p.: 97-98 °C), **IVd** m.p.: 91 °C (Ref. 14 m.p.: 90-91 °C), **IVe** m.p.: 72 °C (Ref. 13 m.p.: 68.5-70.5 °C), **IVf** m.p.: 117 °C (Ref. 13 m.p.: 117-118 °C)].

Synthesis of compounds Va-f

A mixture of 4-chloro-2-piperidin-1yl-thiazole-5-carbaldehyde (**III**) (0.001 mol) and **IVa-f** (0.001 mol) was heated at 130-140 °C in the presence of 0.5 mL of acetic acid glacial and sodium acetate (0.001 mol) for 5 h. The reaction mixture was extracted with $CHCl_3$ (3 × 50 mL) and the organic layer was washed with water, dried over anhydrous Na_2SO_4 and evaporated to dryness. The residue was purified by column chromatography silica gel 60 (230-400 mesh ASTM) using hexane:dichloromethane (1:1) as eluent.

***3-Benzyl-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene)-thiazolidine-2,4-dione* (Va)**

React. Time: 21 h, Yield: 27.47%, m.p.: 151 °C, IR (KBr) cm^{-1}: 1733 (C^4=O), 1685 (C^2=O), ^1H NMR (DMSO-d_6): δ= 1.62 (s, 6H, a), 3.57 (s, 4H, b), 4.80 (s, 2H, CH_2), 7.28-7.36 (m, 5H, Ar-H), 7.80 (s, 1H, =CH), MS (ESI) m/z (rel. intensity): 420 (M+H, 90%).

Anal. for $C_{19}H_{18}ClN_3O_2S_2$: Calc. C: 54.34, H: 4.32, N: 10.01, S: 15.27. Found C: 54.35, H: 4.29, N: 9.84, S: 15.25.

***3-(4-Fluoro-benzyl)-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene)-thiazolidine-2,4- dione* (Vb)**

React. Time: 5 h, Yield: 34.10%, m.p.: 152 °C, IR (KBr) cm^{-1}: 1735 (C^4=O), 1686 (C^2=O), ^1H NMR (DMSO-d_6): δ= 1.62 (s, 6H, a), 3.56 (s, 4H, b), 4.79 (s, 2H, CH_2), 7.16-7.21 (m, 2H, 2', 6'-H), 7.34-7.37 (m, 2H, 3', 5'-H), 7.78 (s, 1H, =CH), MS (ESI) m/z (rel. intensity): 438 (M+H, 90%). Anal. for $C_{19}H_{17}ClFN_3O_2S_2$: Calc. C: 52.11, H: 3.91, N: 9.59, S: 14.64. Found C: 52.12, H: 3.88, N: 9.71, S: 14.43.

***3-(4-Chloro-benzyl)-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene)-thiazolidine-2,4-dione* (Vc)**

React. Time: 8 h, Yield: 45.74%, m.p.: 137 °C, IR (KBr) cm^{-1}: 1740 (C^4=O), 1681 (C^2=O), ^1H NMR (DMSO-d_6): δ= 1.62 (s, 6H, a), 3.57 (s, 4H, b), 4.79 (s, 2H, CH_2), 7.32 (d, 2H, 2', 6'-H), 7.42 (d, 2H, 3', 5'-H), 7.78 (s, 1H, =CH), MS (ESI) m/z (rel. intensity): 454 (M+H, 90%). Anal. for $C_{19}H_{17}Cl_2N_3O_2S_2$: Calc. C: 50.22, H: 3.77, N: 9.25, S: 14.11. Found C: 50.12, H: 3.69, N: 9.24, S: 14.48.

3-(4-Bromo-benzyl)-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene)-thiazolidine-2,4-dione (Vd)

React. Time: 9 h, Yield: 71.67%, m.p.: 169 °C, IR (KBr) cm^{-1}: 1739 (C^4=O), 1679 (C^2=O), ^1H NMR (DMSO-d_6): δ= 1.63 (s, 6H, a), 3.57 (s, 4H, b), 4.78 (s, 2H, CH_2), 7.26 (d, 2H, 2', 6'-H), 7.55 (d, 2H, 3', 5'-H), 7.79 (s, 1H, =CH), MS (ESI) m/z (rel. intensity): 498 (M+H, 65%). Anal. for $C_{19}H_{17}BrClN_3O_2S_2$: Calc. C: 45.75, H: 3.43, N: 8.42, S: 12.86. Found C: 45.28, H: 3.29, N: 8.46, S: 12.66.

3-(2,4-Dichloro-benzyl)-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene)-thiazolidine-2,4-dione (Ve)

React. Time: 13 h, Yield: 54.27%, m.p.: 217 °C, IR (KBr) cm^{-1}: 1734 (C^4=O), 1677 (C^2=O), ^1H NMR ($CDCl_3$): δ= 1.71 (s, 6H, a), 3.59 (s, 4H, b), 4.97 (s, 2H, CH_2), 7.13 (d, 1H, $j_{2',3'}$=8.80 Hz, 2'-H), 7.20 (dd, 1H, $j_{3',2'}$=8.40 Hz, $j_{3',5'}$=2.00 Hz, 3'-H), 7.39 (d, 1H, $j_{5',3'}$=2.00 Hz, 5'-H), 8.04 (s, 1H, =CH), MS (ESI) m/z (rel. intensity): 488 (M+H, 18%).

Anal. for $C_{19}H_{16}Cl_3N_3O_2S_2$: Calc. C: 46.68, H: 3.30, N: 8.60, S: 13.12. Found C: 46.54, H: 3.24, N: 8.46, S: 12.68.

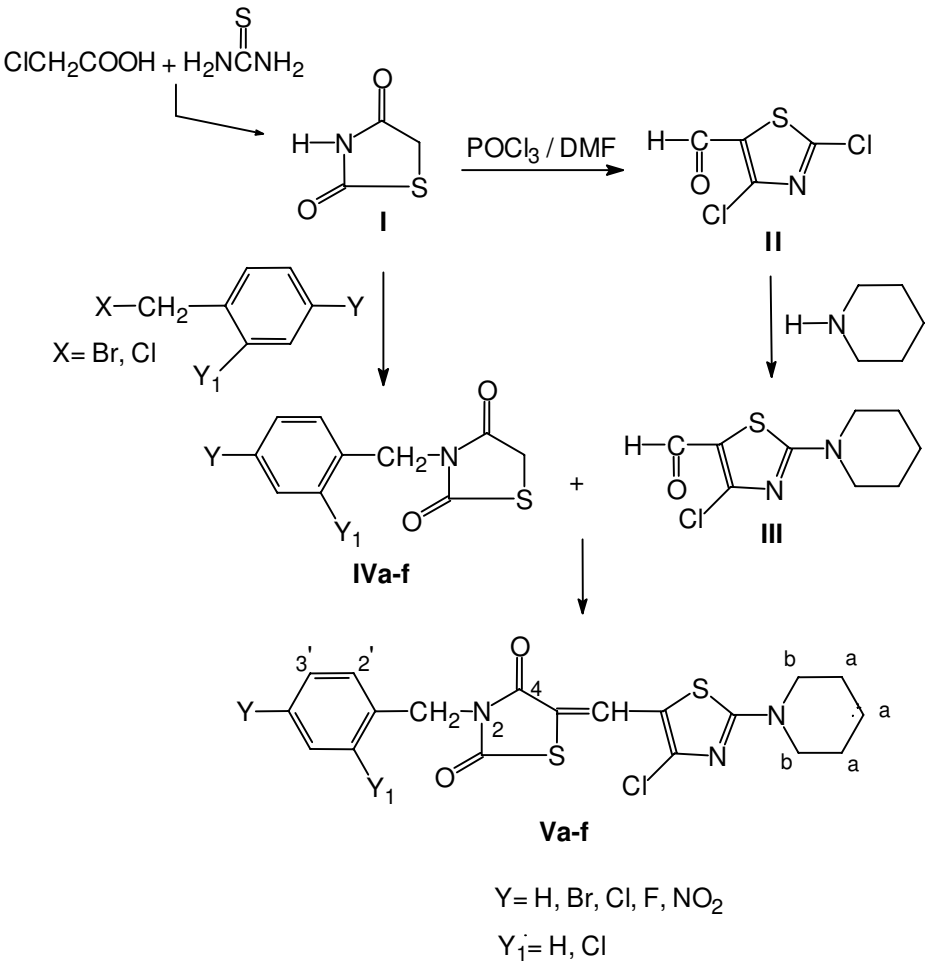
3-(4-Nitro-benzyl)-5-(4-chloro-2-piperidin-1yl-thiazole-5-yl-methylene)-thiazolidine-2,4- dione (Vf)

React. Time: 19 h, Yield: 59.55%, m.p.: 197 °C, IR (KBr) cm^{-1}: 1729 (C^4=O), 1666 (C^2=O), ^1H NMR (DMSO-d_6): δ= 1.63 (s, 6H, a), 3.58 (s, 4H, b), 4.95 (s, 2H, CH_2), 7.57 (d, 2H, 2', 6'-H), 7.81 (s, 1H, =CH),

8.21 (d, 2H, 3', 5'-H), MS (ESI) m/z (rel. intensity): 465 (M+H, 90%). Anal. for $C_{19}H_{17}ClN_4O_4S_2$: Calc. C: 49.08, H: 3.69, N: 12.05, S: 13.79. Found C: 48.69, H: 3.61, N: 11.98, S: 14.11.

Antimicrobial activity

The disk diffusion method was used for assessing antibacterial activity against *Staphylococcus aureus* ATCC 250 (American Type Culture Collection, Manassas, VA, USA), and *Escherichia coli* RSKK 313 (Refik Saydam Kültür Kolleksiyon, Ankara, Turkey), and antifungal activity against *Candida albicans* RSKK 628 (Refik Saydam Kültür Kolleksiyon, Ankara, Turkey). Cultures of each bacteria and yeast strain, kept in Mueller-Hinton broth (Difco, Detroit, MI, USA) at 37 °C for 18-24 h and diluted with the same broth to 10^5 cfu/mL, were pipetted into Mueller-Hinton agar (Difco) plates prepared according to the following procedure. Paper disks (8 mm in diameter) embedded into 3000 μg/mL compound solution were put onto the surface of the inoculated plates, which were placed in an incubator at 37 °C for 18-24 h and then examined. Most of the compounds were found to be effective against the tested microorganisms by measuring the diameter of the growth inhibition zone according to Bauer et al.[15].



Scheme. General synthesis of **Va-f**.

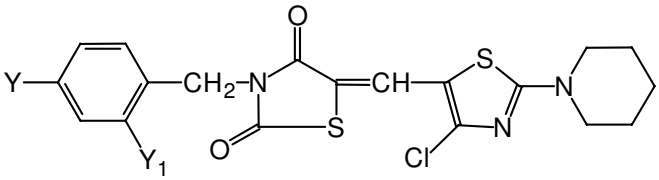
Results and Discussion

2,4-TZD (**I**) was synthesized with $ClCH_2COOH$ and thiourea in hot water[2]. 2,4-Dichlorothiazole-5-carbaldehyde (**II**) was obtained with 2,4-TZD (**I**) and N,N-dimethylformamide in phosphoryl chloride[11]. 4-Chloro-2-piperidin-lyl-thiazole-5-carbaldeyde (**III**) was prepared with 2,4-dichlorothiazole-5-carbaldehyde (**II**) and piperidine in acetonitrile/potassium carbonate[12]. Substituted benzyl-2,4-thiazolidinediones (**IVa-f**)[2,13,14] were obtained by 2,4-TZD (**I**) with appropriate benzyl halide derivatives in NaOH/ethanol. Thiazolyl-2,4-thiazolidinediones (**Va-f**) were prepared via a Knoevenagel reaction between the 4-chloro-2-piperidin-1yl-thiazole-5-carbaldehyde (**III**) and appropriate substituted-2,4-thiazolidinedione (**IVa-f**) in the presence of sodium acetate/acetic acid glacial (Scheme).

The structure of the synthesized thiazolylthiazolidinedione compounds was elucidated by elementary analysis, ^1H NMR, Mass and IR findings. All spectral data were in accordance with the assumed structures. IR spectra of the compounds (**Va-f**) showed 2,4-TZD $C^4 = O$ and $C^2{=}O$ stretching bonds at 1729-1740 cm^{-1} and 1666-1686 cm^{-1}, respectively. In ^1H NMR spectra, benzylic CH_2 protons were seen at 4.78-4.97 ppm as a singlet. Aromatic protons were observed at 7.13-8.21 ppm; methylene protons of thiazolyl-2,4-TZDs were seen at 7.78-8.04 ppm as a singlet. In mass spectra, all the compounds have an M+H ion peak with the MS ESI method.

All of the new thiazolyl-2,4-thiazolidinedione compounds were tested for their antimicrobial activity by the agar diffusion method[15], using *Candida albicans*, *Staphylococcus aureus, Bacillus subtilis* and *Escherichia coli*, and comparing with miconazole and ampicillin (Table). The resulting inhibition zones against *Bacillus subtilis*, *Staphylococcus aureus* and *Escherichia coli* were 10-12, 9-14 and 9-13 mm, respectively. As seen in the Table, compounds (**Va-b, Vd-f**) showed high activity against *Escherichia coli* (12, 11, 10, 11, 10 and 13 mm, respectively) comparable to ampicillin (10 mm). Compounds (**Va-f**) were found to be inactive against *Candida albicans.* The starting carbaldehyde compound (**III**) for (**Va-f**) was active against all the microorganisms tested.

Table. Antimicrobial activities [a)] of the compounds **Va-f**.



Compound	Y	Y_1	*C. albicans*	*S. aureus*	*E. coli*	*B. subtilis*
Va	H	H	*	10	12	10
Vb	F	H	*	9	11	10
Vc	Cl	H	*	12	9	12
Vd	Br	H	*	14	10	11
Ve	Cl	Cl	*	14	11	12
Vf	NO_2	H	*	12	10	12
III			10	12	13	10
Miconazole			25	-	-	-
Ampicillin			-	22	10	23

[a)]Growth inhibition diameter (mm). *No activity. - Not tested

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