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Synthesis, Characterization and Antifungal Activity of Some Substituted 4-thiazolidinone Derivatives

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ABSTRACT

A series of 4-thiazolidinone derivatives was prepared including 2-(4-phenyl)-3-(4-hydroxyphenyl)thiazolidinone-4-one (**1**), 2-(4-bromophenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (**2**), 2-(4-chlorophenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (**3**), 2-(4-methylphenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (**4**), 2-(4-metoxyphenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (**5**), 2-(4-nitrophenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (**6**), 2,3-bis(4-hydroxyphenyl) thiazolidinone-4-one (**7**) and 2-(4-ethyl phenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (**8**). The chemical structures of prepared compounds have been characterized by Mass, IR, ^{1}H-NMR, and elemental analyses. The biological activity of these compounds as fungicides was tested against three commercially known fungicides (*C. albicans*, patient isolate *C. glabrata* and *C. krusei*). The biological activity of compound (**6**) was found to be comparable to that of the commercially available fungicides.

Key word: 4-thiazolidinone derivatives, biological activity, elemental analyses, antifungal

INTRODUCTION

Thiazolidinones derivatives belong to an important group of heterocyclic compounds [1]. Thiazolidinones, with a carbonyl group in position 2, 4, or 5, have been subject of extensive study in the recent past [2]. Numerous reports have appeared in the literature which highlight their chemistry and use [3]. Chemical and biological activities of heterocyclic compounds have been extensively investigated for many years due to the different pharmacological aspects [4]. Several heterocyclic compounds containing sulfur and nitrogen atoms possess a broad spectrum of biological activities [2,3]. 4-Thiazolidinone derivatives are found in numerous natural products [5]. It is known that heterocyclic compounds are the most prescribed antibiotics [6]. These compounds are considered an important contribution to our life. Many organic compounds containing nitrogen and sulfur atoms, i.e., 4-thiazolidinone derivatives have a wide spectrum of biological activities [7].

There are different methods for the preparation of 4-thiazolidinone derivatives. All attempts were made to find easy, inexpensive and fast methods of preparation with high yields. 4-Thiazolidinone derivatives demonstrated a wide spectrum of biological activities [8]. These activities include anti-inflammatory [9], anti-tubercular [10], anti-bacterial [11], anti-convulsant [12], and anthelmintic activity [13]. 4-Thiazolidinone derivatives preparation is well known by various methods [14-16]. The classical method involves a base catalyzed condensation of chalcone with hydroxylamine hydrochloride between Schiff-bases and

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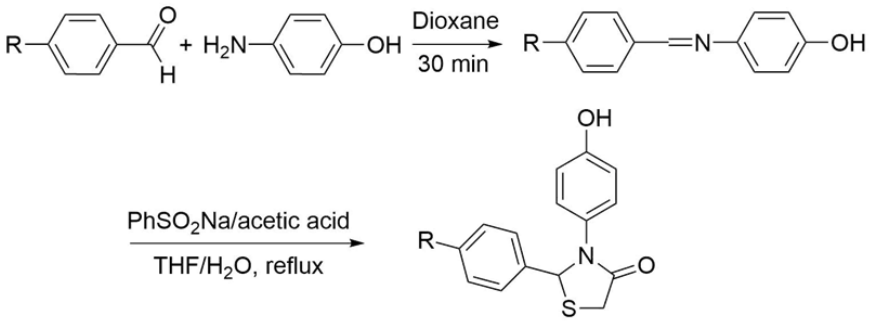
mercaptoacetic acid [17]. Another method involves the cyclo-condensation reactions [18]. One pot preparation method of these compounds was discussed in literature [19]. In this paper, we report the synthesis and characterization of 4-thiazolidinone derivatives, using a simple and rapid method. Anti-fungal activity of synthesized compounds was discussed.

EXPERIMENT

All chemical reagents used in this study were purchased from Aldrich (Milwaukee, WI, USA) and E. Merck Darmstadet, Germany. All solvents were purified according to standard procedures. All of the synthesized 4-thiazolidinone derivatives (**1-8**) were analyzed by Mass, IR, ^{1}H-NMR and elemental analysis. Mass spectra were recorded on Shimadzu LCMS 2010A. IR spectra were recorded on Nicolet 740 Fourier Transform Infrared (FTIR) spectrometer. ^{1}H-NMR-spectra were recorded on a Varian Gemini 200 and 300 MHz instrument in $CDCl_3$ and DMSO-d_6 using Tetra methyl silane (TMS) as an internal standard. Melting Points were measured using a Buchi-510 apparatus and were uncorrected. All instrumental analyses were performed at Bin Hayyan Laboratory (Aqaba Special Economic Zone-Jordan).

Experimental procedure for the preparation of 4-thiazolidinone derivatives (1-8)

A 0.01 mole of 4-aminophenol was added dropwise at room temperature to 0.01 mole of 4-bromobenzaldehyde in 50 ml dioxane over 30 minutes, yielding 4-(4-bromo benzilidene amino) phenol. About 1.4 g (0.05mol) of obtained product, 50 ml $PhSO_2Na$/acetic acid in 100 ml water and 0.01 mole of THF were taken in a 250 ml round-bottomed flask. The reaction mixture was stirred for 1 hour then refluxed for 6 hours at 50 ^oC. After completion of reaction confirmed by TLC (eluent hexane/ethyl acetate 30:70), the solvent was removed under reduced pressure and extracted in 50 ml ethyl acetate. Organic layer was washed in 20-30 ml of water and then dried over sodium bicarbonate. The precipitate was filtered off and purified by recrystallization from ethanol yielding 2-(4-bromo phenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (**2**). Using the same protocol, other derivatives were prepared as shown in Scheme 1 with 80-95% yields.



Scheme 1. Reaction for preparation of compounds (**1-8**) in this study, where R=4-H, 4-Br, 4-Cl, 4-CH_3, 4-OCH_3, 4-NO_2, 4-OH, 4-C_2H_5

Spectral data for 4-thiazolidinone derivatives (1-8)

2-(4-phenyl)-3-(4-hydroxyphenyl)thiazolidinone-4-one (1)

Molecular formula ($C_{15}H_{13}NO_2S$), yield: 80%, m.p: 165-167; MS (m/z): M^+ calculated: 271.33, found: 271.06; IR (KBr, cm^{-1}): 620 (C-S), 1345 (C-N), 1655 (C=O), 3165.5 (C-OH). ^{1}H NMR (DMSO-d_6): δ (ppm) = 4.1 (3H, Ar-C-N), 5.95 (1H, S), 2.65 (3H, N), 5.24 (1H, N-

CH), 5.70 (1H, C-OH), 7.15 (3H, Ar-H, J=10Hz), 7.65 (2H, Ar-H, J=10Hz). Elem. anal. Calculated: C: 66.39%, H: 4.83%, N: 5.15%, Found: C: 66.18%, H: 4.68%, N: 5.01%.

2-(4-bromophenyl)-3-(4-hydroxyphenyl)thiazolidinone-4-one (2)

Molecular formula ($C_{15}H_{12}BrNO_2S$), yield: 84%, m.p: 182-184; MS (m/z): M^+ calculated: 350.23, found: 350.03 IR (KBr, cm^{-1}): 652 (C-Br str.),620 (C-S), 1345 (C-N), 1655 (C=O), 3165.5 (C-OH). ^1H NMR (DMSO-d_6): δ (ppm) = 4.1 (3H, Ar-C-N), 5.95 (1H, S), 2.65 (3H, N), 5.24 (1H, N-CH), 5.70 (1H, C- Br), 5.70 (1H, C-OH), 7.15 (3H, Ar-H, J=10Hz), 7.65 (2H, Ar-H, J=10Hz). Elem. anal. Calculated: C: 51.43%, H: 3.45%, N: 3.99%, Found: C: 51.65%, H: 3.68%, N: 3.77%.

2-(4-chlorophenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (3):

Molecular formula ($C_{15}H_{12}ClNO_2S$, yield: 90%, m.p: 166-168; MS (m/z): M^+ calculated: 305.78, found: 305.21 IR (KBr, cm^{-1}): 1309 (C-Cl str.), 621 (C-S), 1348 (C-N), 1644 (C=O), 3160 (C-OH). ^1H NMR (DMSO-d_6): δ (ppm) = 4.1 (3H, Ar-C-N), 5.92 (1H, S), 2.67 (3H, N), 5.24 (1H, N-CH), 5.56 (1H, C-Cl), 5.70 (1H, C-OH), 7.15 (3H, Ar-H, J=10Hz), 7.65 (2H, Ar-H,J=10Hz). Elem. anal. Calculated: C: 58.91%, H: 3.96%, N: 4.57%, Found: C: 68.66%, H: 3.78%, N: 4.32%.

2-(4-methylphenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (4)

Molecular formula ($C_{16}H_{15}NO_2S$), yield: 86%, m.p: 155-157; MS (m/z): M^+ calculated: 285.36, found: 284.96 IR (KBr, cm^{-1}): 625 (C-S), 1345 (C-N), 1634 (C=O), 3160 (C-OH). ^1H NMR (DMSO-d_6): δ (ppm) = 4.1 (3H, Ar-C-N), 5.88 (1H, S), 1.90 (3H, CH_2), 5.21 (1H, N-CH), 5.70 (1H, C-OH), 7.15 (3H, Ar-H, J=10Hz), 7.65 (2H, Ar-H, J=10Hz). Elem. anal. Calculated: C: 63.13%, H: 5.31%, N: 4.91%, Found: C: 63.22%, H: 5.18%, N: 4.98%.

2-(4-metoxyphenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (5)

Molecular formula ($C_{16}H_{15}NO_3S$), yield: 95%, m.p: 124-126; MS(m/z): M^+ calculated: 301.36, found: 301.03 IR (KBr, cm^{-1}): 638 (C-S), 1345 (C-N), 1614 (C=O), 1210 (C-O str.) 3150 (O-H). ^1H NMR (DMSO-d_6): δ (ppm) = 4.1 (1H, Ar-C-N), 5.95 (1H, S), 1.91 (3H, CH_2), 3.80 (3H, OCH_3), 2.67 (3H, N), 5.24 (1H, N-CH), 5.40 (1H, Ar-OH), 7.15 (3H, Ar-H, J=10Hz), 7.65 (2H, Ar-H, J=10Hz). Elem. anal. Calculated: C: 63.76%, H: 5.03%, 4.64%, Found: C: 63.60%, H: 4.98%, N: 4.54%.

2-(4-nitrophenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (6)

Molecular formula ($C_{15}H_{12}N_2O_4S$), yield: 80%, m.p: 187-189; MS (m/z): M^+ calculated: 316.33, found: 316.05. IR (KBr, cm^{-1}): 640 (C-S), 1345 (C-N), 1614 (C=O), 1210 (C-O str.), 3430-3445 (N-H str.). ^1H NMR (DMSO-d_6): δ (ppm) = 4.1 (1H, Ar-C-N), 1.91 (3H, CH_2), 5.24 (1H, N-CH), 5.70 (1H, C-OH), 7.15 (3H, Ar-H, J=10Hz), 7.65 (2H, Ar-H, J=10Hz) Elem. anal. Calculated: C: 56.95%, H: 3.83%, N: 8.85%, Found: C: 56.48%, H: 3.59%, N: 8.30%.

2,3-bis(4-hydroxyphenyl) thiazolidinone-4-one (7)

Molecular formula ($C_{15}H_{13}NO_3S$), yield: 88%, m.p: 231-233; MS (m/z): M^+ calculated: 287.33, found:: 287.01. IR (KBr, cm^{-1}): 651 (C-S), 1344 (C-N), 1615 (C=O), 3450 (O-H str.). ^1H NMR (DMSO-d_6): δ (ppm) = 4.1 (1H, Ar-C-N), 1.90 (3H, CH_2), 2.67 (2H, CH_3-N), 5.24 (1H, -N-CH-C), 5.40(2H, Ar-OH), 7.15 (3H, Ar-H, J=10Hz), 7.65 (2H, -Ar-H, J=10Hz).

Elem. anal. Calculated: C: 62.69%, H: 4.56%, N: 4.87%, Found: C: 62.42%, H: 4.50%, N: 4.39%.

2-(4-ethylphenyl)-3-(4-hydroxyphenyl) thiazolidinone-4-one (8)

Molecular formula ($C_{17}H_{17}NO_2S$), yield: 82%, m.p: 136-138; MS (m/z): M^+ calculated: 299.39, found: 299.29. IR (KBr, cm^{-1}): 625 (C-S), 1345 (C-N), 1634 (C=O), 3160 (C-OH). ^{1}H NMR (DMSO-d_6): δ (ppm) = 4.1 (3H, Ar-C-N), 5.88 (1H, S), 1.90 (3H, CH_2), 5.21 (1H, N-CH), 5.70 (1H, -C-OH), 7.15 (3H, Ar-H, J=10Hz), 7.65 (2H, -Ar-H, J=10Hz). Elem. anal. Calculated: C: 68.19%, H: 5.73 %, N: 4.67%, Found: C: 68.10%, H: 5.48%, N: 4.28%.

Antifungal activity

The anti-fungal activity of the synthesized compounds was determined against three commercially known fungicides (*C. albicans*, patient isolate *C. glabrata* and *C. krusei*) by measuring minimum inhibitory concentration (MIC), expressed in µg/ml. The yeasts were grown on Sabouraud Dextrose Broth (Difco) media; the yeasts were incubated for 48 h at room temperature. The antifungal activity tests were carried out at pH (7.5) in Sabouraud Dextrose Broth and the 2-fold dilution was applied. A set of tubes containing only inoculated broth were kept as controls. The *in vitro* antifungal activity of the compounds was tested by the tube dilution technique [20]. Each of the test compounds and standards Miconazole and Fluconazole were dissolved in 10% DMSO, at concentrations of 100 µg/ml. Further dilutions of the compounds and standards in the test medium were performed at the required quantities of 50, 25, 12.5, 6.25, 3.12, 1.56, 0.78 µg/ml concentrations. The final concentration was 10^5 CFU/ml. The MICs were defined as the lowest concentration of the compounds that prevented visible growth of the fungus. It was determined that the solvent had no antifungal activity against any of the test microorganisms (Table 1).

Table 1 Results of the *in vitro* antifungal activity of the prepared compounds **1-8**, (MIC, µg/ml).

Compound No.	*C. albicans*	C. *glabrata*	*C. krusei*
1	22	23	10.50
2	25	22	11.75
3	21	22	11.55
4	20	25	12.45
5	25	23	11.50
6	12.5	256.	6.25
7	22	23	12.00
8	20	21	11.85
Miconazole	6.25	3.125	1.56
Fluconazole	12.5	3.125	3.125

RESULT AND DISCUSSION

Reaction of 4-aminophenol with 4-substitutes benzaldehyde in dioxane at room temperature obtained 4-(4-substitutes benzylidene amino) phenol. The obtained products reacted with $PhSO_2Na$/acetic acid using THF as solvent to give 2-(4-substitutes phenyl)-3-(4-hydroxyphenyl)thiazolidinone-4-one (**1-8**) in good yields. Synthesized compounds were confirmed by TLC, IR, ^{1}H-NMR, and elemental analysis. Melting points (m.p) have been identified for each of these compounds.

Mass spectra showed the molecular weights apart from fragmentation profile. The spectra data (IR, ^{1}H-NMR) confirmed the formation of 2-(4-substitutes phenyl)-3-(4-hydroxyphenyl)thiazolidinone-4-one (**1**-**8**). All compounds are stable solids; dissolve in DMSO at room temperature. The titled compounds were confirmed by IR spectral data showing characteristic peaks at 1621(C-S), 1348 (C-N), 1644 (C=O), 3160 (C-OH). The ^{1}H-NMR spectra of the synthesized compounds showed characteristic peaks δ (ppm) = 4.1 (3H, Ar-C-N), 5.92 (1H, S), 2.67 (3H, N), 5.24 (1H,N-CH), 5.70 (1H-C-OH). All of the compounds were tested for their in *vitro* growth inhibitory activity against *C. albicans*, patient isolate *C. glabrata* and *C. krusei* (Table 1). Compound **6** possessed comparable activity to Fluconazole against *C. albicans* with a MIC of 12.5µg/ml. None of the compounds was superior to the standards used against any fungus.

CONCLUSION

In this study, we synthesized some derivatives of 4- thiazolidinone and studied their antifungal activity. The yields of synthesized compounds were in the range of 80-95%.The purity of the synthesized compounds was assessed by TLC and melting points. Compound **6** showed biological activity comparable to Fluconazole against *C. albicans*. As a result, we have come to the conclusion that electron withdrawing groups decrease the biological activity of the synthesized compounds.

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