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Research Article

SYNTHESIS & ANTIMICROBIAL ACTIVITY OF A NEW SERIES OF 3, 5-DISUBSTITUTED THIAZOLIDINE-2, 4-DIONES

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ABSTRACT

A new series of 3-aryl-5-arylidine thiazolidine-2, 4-dione derivatives have been synthesized & evaluated for their antimicrobial activity. The purity of the synthesized compounds was confirmed by their physical constant and TLC. The structure of the synthesized compounds was confirmed by IR, NMR & mass spectral data. The inhibitory activity of the synthesized compounds 3(a-i) was studied which is expressed as minimum inhibitory concentration (MIC) in µg/ml. All compounds were found moderately active.

Keywords: 3,5-disubstituted thiazolidine-2,4-dione, Antibacterial and antifungal activity, Broth micro-dilution method, Minimum Inhibitory Concentration.

INTRODUCTION

Thiazolidinediones have been the subjects of extensive researchers because of their deep involvement in the regulation of different physiological processes.1 Heterocyclic compounds containing Nitrogen & Sulfur possess wide variety of pharmacological activities. Thiazolidine-2,4-dione possess pharmacological activities such as anticonvulsants[2] and antibacterials.[3] They are also known to possess tuberculostatic[4] and antitumor[5] activity. Thiazolidinediones, also known as "glitazones," are sometimes referred to as insulin enhancers.[6] A number of thiazolidine-2,4-dione based molecule such as Triglitazone, Englitazone, Pioglitazone, Rosiglitazone etc have shown potential activities and are used as clinical anti-diabetic agents.[1] It is known that a heterocycle containing a carbonyl group is more efficacious than a simple heterocycle.[7] We have synthesized a new series of thiazolidine-2,4-dione derivatives for the antimicrobial activities.

MATERIALS & METHODS

Materials & Reagents:

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points of synthesized compounds were determined using open capillary tube and are uncorrected. All reactions were monitored by thin-layer chromatography (TLC) on 0.25 mm silica gel (60GF-254) plates and visualized with UV light.IR spectra were recorded on Thermo Nicolet spectrophotometer by using KBr pellets. The ^{1}H-NMR was recorded on Bruker Avance II NMR 400 MHz instruments using DMSO as solvent and TMS as internal standard, chemical shifts are expressed as δ values (ppm).

Synthesis

Synthesis of Thiazolidine-2, 4-dione[8] (1)

In a 250 ml three necked round-bottomed flask was place, solution containing (56.4 gm, 0.6 mol) of chloro-acetic acid in 60 ml of water and (45.6 gm, 0.6 mol) of thiourea dissolved in 60 ml of water. The mixture was stirred for 15 min to form a white precipitate, accompanied by considerable cooling. To the contents of the flask was then added slowly 60 mL of concentrated hydrochloric acid from a dropping funnel, the flask was then connected with a reflux condenser and gentle heat applied to effect complete solution, after which the reaction mixture was stirred and refluxed for 8-10 hrs at 100-110°C. On cooling the contents of the flask solidified to a cluster of white needles. The product was filtered and washed with water to remove traces of hydrochloric acid and dried. It was purified by re-crystallization from ethyl alcohol. Yield: 85%, mp: 123 °C. The physical data and spectral data of the synthesized compound (1) is depicted in Table 1 and 2.

Synthesis of 5-arylidine thiazolidine-2,4-dione[9] (2a - 2c)

Equimolar amount of various aldehyde and 2,4-thiazolidinedione (I) were refluxed in absolute ethanol for 4 hours in the presence of catalytic amount of piperidine. The reaction mixture was cooled and poured on to crushed ice with stirring. The solid product was washed with toluene and dried to give 5-benzylidine-2,4-thiazolidinedione. It was purified by re-crystallization from ethyl alcohol. The physical data and spectral data of the synthesized compound (II a –II b) is depicted in Table 1 and 2.

Synthesis of 3-aryl-5-arylidine thiazolidine-2, 4-dione[10] (3a - 3i)

A solution of 0.8g of Sodium hydroxide (0.02 mol) was made in 20 ml ethanol. To this solution, 5-benzylidine-2, 4-thiazolidinedione (II a –II c) (0.02 mol) and substituted benzyl chloride (0.02 mol) were added. The resulting reaction mixture was then refluxed for 48-50 hours. Precipitation of salt was observed during the reaction. At the end of the reflux period, ethanol was distilled out and the residue was extracted with ether and water. The ethereal layer was removed, dried over magnesium sulphate. The product was dried under reduced pressure and was re-crystallized from ethanol. The physical data and spectral data of the synthesized compound (III a – III i) is depicted in Table 1 and 2.

Antimicrobial activity

For the antibacterial and antifungal activity, the compounds were dissolved in dimethylsulfoxide (DMSO). Further dilutions of the compounds and standard drugs in the test medium were prepared at the required quantities of 256, 128, 64, 32, 16, 8, 4, 2, 1 µg/ml concentrations with Mueller–Hinton broth and Sabouraud dextrose broth. The minimum inhibitory concentrations (MIC) were determined using the twofold serial dilution technique (National Committee for Clinical Laboratory Standards, 2000). A control test was also performed containing inoculated broth supplemented with only DMSO at the same dilutions used in our experiments and found inactive in the culture medium. All the compounds were tested for their in vitro growth inhibitory activity against different bacteria and fungi.

Antibacterial and antifungal activity

The cultures were obtained from Mueller–Hinton broth for all the bacterial strains after 24 h of incubation at 37 ± 1 ^{0}C. Fungi were maintained in Sabouraud dextrose broth after incubation for 24 h at 25 ±1 ^{0}C. Testing was carried out in Mueller–Hinton broth and Sabouraud dextrose broth at pH 7.4 and the twofold serial dilution technique was applied. The final inoculum size was 105 CFU/ml for the antibacterial assay and 104 CFU/ml for the antifungal assay. A set of tubes containing only inoculated broth was used as controls. For the antibacterial assay after incubation for 24 h at 37± 1 ^{0}C and

after incubation for 48 h at 25± 1 ^{0}C for antifungal assay, the tube with no growth of microorganism was recorded to represent the MIC expressed in µg/ml. Every experiment in the antibacterial and antifungal assay was replicated twice.

RESULTS AND DISCUSSION

The main aim of this work was to synthesize substituted 3-aryl-5-arylidine thiazolidine-2, 4-diones. Initially, Thiazolidine-2,4-dione (1) was synthesized by condensation of Thiourea and Chloroacetic acid in presence of Conc. Hydrochloric acid. The substituted 5-benzylidine-2,4-thiazolidinediones (2a–2c) were synthesized from reaction of thiazolidine-2,4-dione (1) and corresponding aromatic aldehydes in presence of piperidine. The titled compounds (3a–3i) were obtained by the reaction of substituted 5-benzylidine-2,4-thiazolidinedione (2a–2c) and corresponding substituted benzyl halide in presence of sodium hydroxide.

The structures of newly synthesized compounds (3a–3i) were confirmed by their spectral data. IR spectra of above compounds (3a–3i) showed sharp bands around 1600-1640 cm^{-1}(-C=O stretch), 3000-3050 cm^{-1}(-CH aromatic stretch), 2830-2860 cm^{-1}(-CH aliphatic stretch), 1590-1610 cm^{-1}(-CN stretch), 3400-3450 cm^{-1}(-OH stretch). This is further supported by 1H-NMR spectral data with δ value at 2.51(1H, s, CH), 4.80(2H, s, CH_2), 10.54(1H, s, OH), 6.91-7.47(8H, m, aromatic protons) reveals the confirmation of structures. Subsequent purification of the final compounds yielded the compounds in moderate to higher yields.

MIC for antibacterial & antifungal activity was determined by broth microdilution method using BHI as media against *Staphylococcus aureus*, *Enterococcus faecalis*, *Escherichia coli* and *Klebsiella pneumoniae* and compared with Ciprofloxacin and Norfloxacin as standard and against *Candida albicans, Aspergillus niger* and *Aspergillus flavus* and compared with Fluconazole and Griseofulvin as standard respectively. MIC showed that many of the compounds were active against the microorganisms in very minimal concentrations.

The compound 3i having electron withdrawing substituent (Cl) at C-15 of the aryl halide and electron releasing substituent (OH) at C-10 of arylidene was found active at lowest concentration of 1µg/ml against gram positive bacteria *Staphylococcus aureus* and *Enterococcus faecalis* and against gram negative bacteria *E.coli* and *K pneumoniae* at concentration of 62.5µg/ml. The compound 3d having electron releasing substituent (OH) at C-8 of arylidene was found active at concentration of 62.5µg/ml against gram negative bacteria *E.coli* and *K pneumoniae.* The compound 3g having electron releasing substituent (OH) at C-10 of arylidene was found active at concentration of 2µg/ml against gram positive bacteria *Staphylococcus aureus* and *Enterococcus faecalis*. The compound 3b having electron withdrawing substituent (Cl) at C-17 of the aryl halide was found active against gram positive bacteria at concentration of 4µg/ml.

The compound 3i having electron withdrawing substituent (Cl) at C-15 of the aryl halide and electron releasing substituent (OH) at C-10 of arylidene was found active at concentration of 4µg/ml against *Candida albicans, Aspergillus niger* and *Aspergillus flavus.* The compound 3b having electron withdrawing substituent (Cl) at C-17 of aryl halide was found active at concentration of 16µg/ml against *Candida albicans, Aspergillus niger* and *Aspergillus flavus.* The compound 3g having electron releasing substituent (OH) at C-10 of arylidene was found active at concentration of 4µg/ml against *Candida albicans*.

Table 1: Physical Data of the Synthesized Compounds

Compounds	R	R^1	Molecular Formula	Molecular Weight	m.p.(^{0}C)	Yield (%)
1	Thiazolidine-2,4-dione	------	$C_3H_3NO_2S$	117	123-25	80.16
2a	H	------	$C_{10}H_7NO_2S$	205	240-42	71.65
2b	2-OH	------	$C_{10}H_7NO_2S$	222	278-80	73.30
2c	4-OH	------	$C_{10}H_7NO_2S$	222	282-85	71.36
3a	H	H	$C_{12}H_{13}NO_2S$	295	210-12	70.75
3b	H	4-Cl	$C_{12}H_{13}NO_2SCl$	329	215-16	71.69
3c	H	2-Cl	$C_{12}H_{13}NO_2SCl$	329	210-13	68.16
3d	2-OH	H	$C_{12}H_{14}NO_3S$	311	240-43	67.68
3e	2-OH	4-Cl	$C_{12}H_{14}NO_3SCl$	345	245-46	70.30
3f	2-OH	2-Cl	$C_{12}H_{14}NO_3SCl$	345	245-47	72.27
3g	4-OH	H	$C_{12}H_{14}NO_3S$	311	250-52	74.45
3h	4-OH	4-Cl	$C_{12}H_{14}NO_3SCl$	345	245-48	68.77
3i	4-OH	2-Cl	$C_{12}H_{14}NO_3SCl$	345	255-57	67.03

Table 2: Spectral Data of the Synthesized Compounds

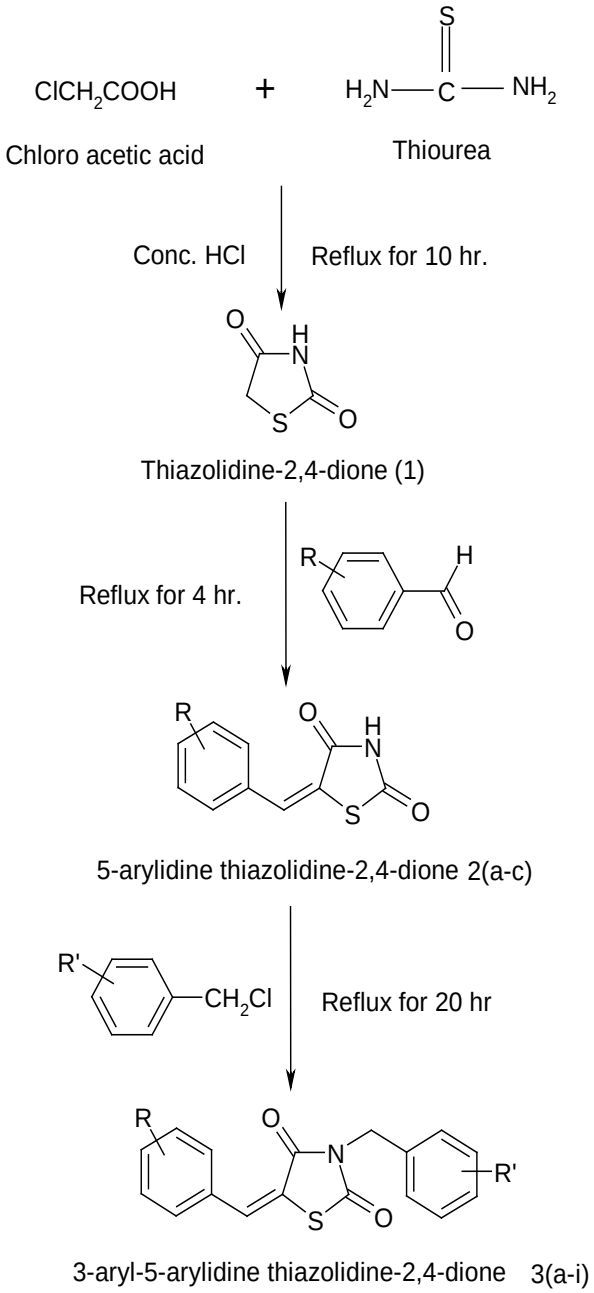
Compounds	IR spectra (KBr cm^{-1})	^{1}H NMR spectra (δ, ppm)	Mass Spectra (m/z value)
1	1673.8(C=O), 1739.9(C=O), 3134.0(N-H).	8.75 (1H, s, NH), 3.72,3.75 (2H, d, CH_2).	------
2a	1691.0(C=O), 1738.3(C=O), 3141.6(N-H), 3034.8(C-H; aromatic)	------	205
2b	1678.3(C=O), 1729.0(C=O), 3137.3(N-H), 3024.0(C-H; aromatic), 3421.9(O-H)	8.54(1H, s, NH), 4.79(1H, s, CH), 8.99(1H, s, OH), 7.29-7.47 (4H, m, aromatic protons).	------
2c	1678.6(C=O), 1723.0(C=O), 3125.2(N-H), 3003.2(C-H; aromatic), 3404.8(O-H)	-------	------
3a	1686.5(C=O), 1735.8(C=O), 3021.7(C-H; aromatic), 1604.5(C-N),	2.46(1H, s, CH), 4.82(2H, s, CH_2), 7.28-7.63 (10H, m, aromatic protons).	-----
3b	1690.2(C=O), 1739.5(C=O), 3035.3(C-H; aromatic), 1608.6(C-N),	2.48(1H, s, CH), 4.89(2H, s, CH_2), 7.25-7.78(9H, m, aromatic protons).	-----
3c	1686.1(C=O), 1740.5(C=O), 3017.2(C-H; aromatic), 1603.9(C-N),	-----	329
3d	1679.2(C=O), 1729.7(C=O), 3038.1(C-H; aromatic), 1592.8(C-N), 3420.8(O-H).	-----	-----
3e	1679.7(C=O), 1730.1(C=O), 3036.0(C-H; aromatic), 1592.7(C-N), 3421.0(O-H).	-----	-----
3f	1665.7(C=O), 1731.3(C=O), 3053.7(C-H; aromatic), 1594.7(C-N), 3420.0(O-H).	2.51(1H, s, CH), 4.80(2H, s, CH_2), 10.54(1H, s, OH), 6.91-7.47(8H, m, aromatic protons).	345
3g	1679.4(C=O), 1723.6(C=O), 3007.2(C-H; aromatic), 1591.0(C-N), 3405.0(O-H).	-----	311
3h	1678.9(C=O), 1724.6(C=O), 3008.8(C-H; aromatic), 1593.1(C-N), 3405.5(O-H).	2.48(1H, s, CH), 4.49(2H, s, CH_2), 10.36(1H, s, OH), 6.89-7.85(8H, m, aromatic protons).	-----
3i	1680.1(C=O), 1724.1(C=O), 3009.1(C-H; aromatic), 1592.1(C-N), 3405.0(O-H).	-----	-----

Table 3: Inhibitory Activity of the Synthesized compounds 3(a-i) Expressed as Minimum Inhibitory Concentration (MIC) in µg/ml

Compounds	R	R¹	S. a	E. f	K. p	E. c	C. a	A. n	A. f
3a	H	H	2	16	500	500	2	8	2
3b	H	4-Cl	4	4	250	500	16	16	8
3c	H	2-Cl	8	8	500	>500	16	16	8
3d	2-OH	H	4	31.25	62.5	62.5	31.25	16	16
3e	2-OH	4-Cl	16	16	62.5	250	31.25	1	8
3f	2-OH	2-Cl	4	8	250	250	16	1	8
3g	4-OH	H	2	4	>500	>500	4	8	8
3h	4-OH	4-Cl	4	62.5	>500	>500	8	8	4
3i	4-OH	2-Cl	1	1	62.5	62.5	4	4	2
Ciprofloxacin			2	2	1	2	NT	NT	NT
Norfloxacin			10	3.1	0.1	10	NT	NT	NT
Fluconazole			NT	NT	NT	NT	16	8	8
Griseofulvin			NT	NT	NT	NT	500	100	7.5

NT, Not Tested; S.a, Staphylococcus aureus; E.f, Enterococcus faecalis; K.p, Klebseilla Pneumonia; E.c, Escherichia coli; C.a, Candida albicans; A.n, Aspergillus niger. P.a, A.f, Aspergillus flavus

SCHEME



Compounds	R	R'
3a	H	H
3b	H	4-Cl
3c	H	2-Cl
3d	2-OH	H
3e	2-OH	4-Cl
3f	2-OH	2-Cl
3g	4-OH	H
3h	4-OH	4-Cl
3i	4-OH	2-Cl

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