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RESEARCH ARTICLE

Synthesis, Characterization and Antimicrobial Activity of 5-Substituted indole-2,3-dione Based 4 -Thiazolidione Derivatives

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Abstract: A series of 5-substituted indole- 2,3-dione based spiro-4-thiazolidiones were synthesized, characterization and evaluated for their antimicrobial activity. Condensation of 5-substituted indole-2,3-dione with substituted primary aryl amine was formed series of Schiff bases (**1**) which on reaction with thioglycolic acid and thiolactic acid in 1,4-dioxane afforded the formation of the corresponding 4-thiazolidinones (**2, 3**). All the synthesized compounds were characterized on the basis of their IR, ^{1}H and ^{13}C NMR and elemental analysis. The antimicrobial activity of all the compounds (D01-D04, E01-E04) showed significant activity against the selected micro organisms.

Keywords: 5-Substituted indole -2,3-dione, Spiro-4-thiazolidiones, Antimicrobial

Introduction

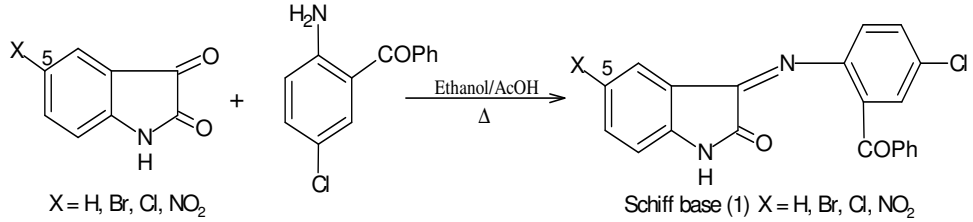
Spirocyclic system containing one carbon atom common to two rings are structurally interesting[1]. Spiro compounds represent an important class of naturally occurring substances and their characteristic is the highly biological properties[2,3]. 1-*H*-indole-2,3-dione, (Isatin) and derivatives possess a broad range of biological and pharmacological properties and are widely used as starting materials for the synthesis of a broad range of heterocyclic compounds and substrates for drug synthesis[4]. It was first prepared by Erdmann and Laurent through the oxidation of indigo by nitric acid and chromic acid[5,6]. Some of its derivatives specifically Haloisatin and Nitroisatin show a wide range of biological and pharmacological activities such as antimicrobial[7-12], anticonvulsant[13,14], analgesic[15,16], anticancer[17,18], anti-tubercular[19], antiviral[20-22] and anti-HIV[23] activities. The literatures survey revealed that introduction of electron withdrawing groups at positions 5, 6 and 7 greatly increased the activities of isatin, with substitution at the 5th position is being most favorable. 4-Thiazolidinones also possess various important biological activities such as antibacterial,

antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, anti inflammatory and analgesic properties[24-26]. Spiro heterocyclic compounds including thiazolidine moiety have antimicrobial activity[27]. Spiroindole heterocyclic, in which the indole ring is linked to the other heterocyclic system through the spirocarbon atom at C-3, show an increased spectrum of biological activities. Systematic investigations of this class of heterocyclic have been carried out by Joshi and co-workers[28].

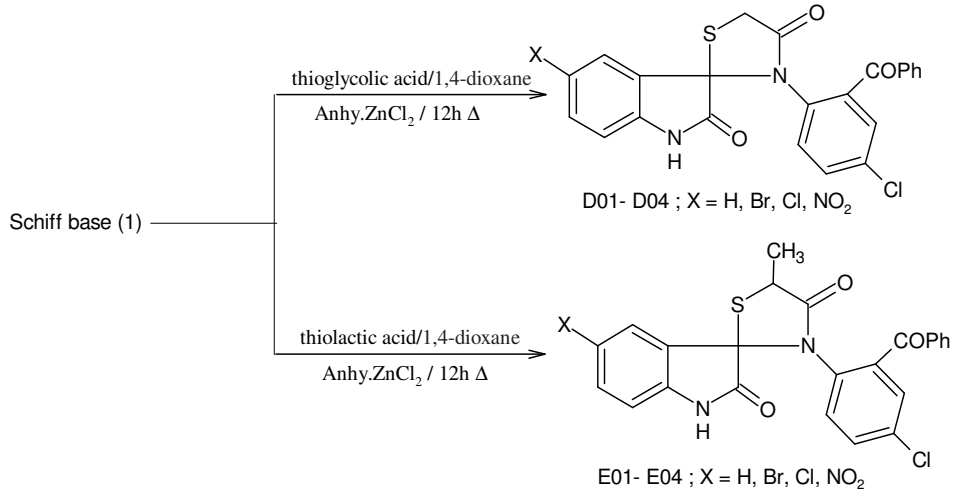
The synthesis, characterization and antimicrobial evaluation of 5-substituted indole-2,3-dione based spiro-4-thiazolidiones have been undertaken as per the scheme mentioned in the experimental section. All the synthesized compounds were characterized on the basis of their physical properties IR, ^{1}H and ^{13}C NMR spectral data and elemental analysis.

Experimental

The melting points were carried out in open capillary tube and were uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate and spots were visualized by exposure to iodine vapour. IR spectra of compounds were scanned on Shimadzu IR spectrophotometer using KBr disc and expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-D_6 on BRUKER spectrometer using TMS as an internal standard (chemical shifts in δ, ppm). The elemental analysis values of C, H, N and S are in good agreement with the calculated values. The 5-substituted Indole-2,3-dione based Schiff bases[29] were prepared from 2-benzoyl-4-chloroaniline in Scheme 1. The synthesis of the target compounds was accomplished according to the reaction sequence illustrated in Scheme 2.



Scheme 1



Scheme 2

Synthesis of 5-substituted indol-2,3-dione based spiro-4-thiazolidiones[30] ***(D01-D04)***

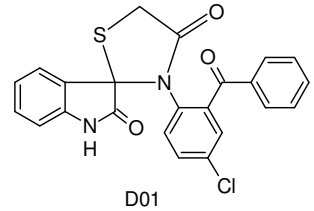
A mixture of Schiff bases[29] (**1**) (0.01 mol) and thioglycolic acid (0.01 mol) was refluxed with 1,4-dioxane for 12 h in the presence of zinc chloride. The completion of reaction was monitored by TLC (Pet ether: ethyl acetate, 3:2). After completion, reaction mixture was poured in ice cold water. The product formed was isolated washed with water and recrystallized from ethanol to give compound **2(D01)**. Similarly other compounds **D02–D04** were synthesized using same procedure.

Synthesis of 5-substituted indol-2,3-dione based 5'-methyl-spiro-4-thiazolidiones[30] ***(E01-E04)***

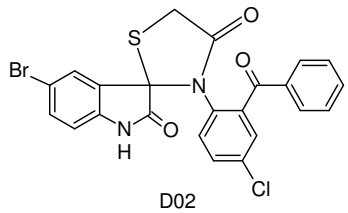
A mixture of Schiff bases[29] (**1**) (0.01 mol) and thiolactic acid (0.01 mol) was refluxed with 1,4-dioxane for 12 h in the presence of zinc chloride. The completion of reaction was monitored by TLC (Pet ether: ethyl acetate, 3:1.5). After completion, reaction mixture was poured in ice cold water. The product formed was isolated washed with water and recrystallized from ethanol to give compound **3(E01)**. Similarly other compounds of **E02–E04** were synthesized using same procedure.

Results and Discussion

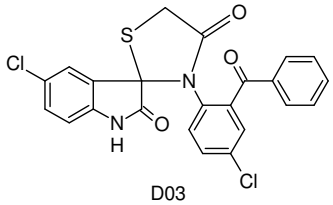
Synthesis of Schiff base was done as mentioned in scheme 1. The required starting material of Schiff base **(A01-A04)** was already confirmed by reported method[29]. It was further on treatment with thioglycolic acid and thiolactic acid yielded the 4-thiazolidinones **(D01–D04; E01–E04)**. The spectral analysis of all the compounds was done by IR, ^{1}H and ^{13}C NMR and the spectral data were consistent with the assigned structures. Figure (**D01–D04, E01–E04**)



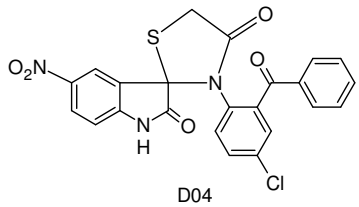
D01



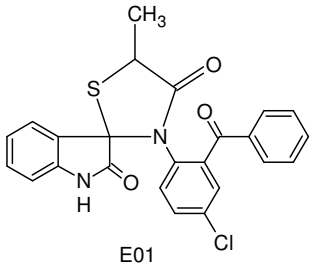
D02



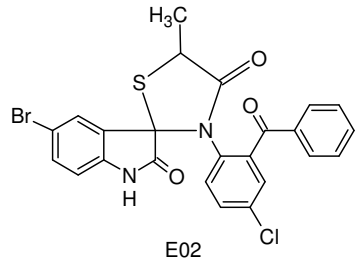
D03



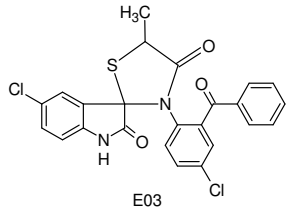
D04



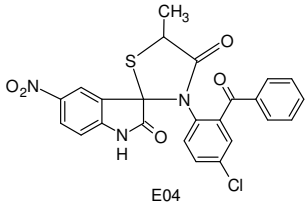
E01



E02



E03



E04

*3'-(2-Benzoyl-4-chlorophenyl)-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (**D01**)*

M.p**:** 203 ^{o}C; IR (KBr) λ_{max} in cm^{-1}: 3417 (N-H str), 3062 (Ar C-H str), 2924 (Ali C-H Str), 1705 (C=O str), 1680 (Spiro C=O), 1612 (N-C=O str), 736 (C-S str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.57 (s, 1H), 7.74-7.70 (t, *J* =7.2 Hz, 1H), 7.64-7.63 (d, *J* =7.6 Hz, 1H), 7.51-7.40 (m, 5H), 7.33-7.30 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.28-7.26 (d, *J* =7.6 Hz, 1H), 7.19-7.18 (d, *J* =2.4 Hz, 1H), 7.08-7.05 (t, *J* =7.6 Hz, 1H), 6.92-6.90 (d, *J* =9.2 Hz, 1H), 3.868 (s, 2H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 196, 184, 174,110-141, 77, 35; Anal. Found: C, 63.52; H, 3.48; N, 6.44; S, 7.36(%). Calc. for ($C_{23}H_{15}ClN_2O_3S$): C, 63.46; H, 3.44; N, 6.43; S, 7.37(%).

*3'-(2-Benzoyl-4-chlorophenyl)-5-bromo-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (**D02**)*

M.p**:** 201 ^{o}C**;** IR (KBr) λ_{max} in cm^{-1}: 3417 (N-H Str), 3062 (Ar C-H Str), 2962 (Ali C-H Str), 1697 (C=O str), 1671 (Spiro C=O), 1606 (N-C=O str), 737 (C-S str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.67 (s, 1H), 7.63-7.60 (dd, *J* =8.4 Hz, 2.4 Hz, 1H), 7.59 (d, *J* =2.4 Hz, 1H), 7.44-7.35 (m, 5H), 7.34-7.31 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.19-7.18 (d, *J* =2.4 Hz, 1H), 6.99-6.97 (d, *J* =8.8 Hz, 1H), 6.93-6.90 (d, *J* =8.8 Hz, 1H), 3.697 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 196, 184, 174, 111–140, 78, 34; Anal. Found: C, 53.77; H, 2.75; N, 5.45; S, 6.24(%). Calc. for ($C_{23}H_{14}ClBrN_2O_3S$): C, 53.71; H, 2.72; N, 5.44; S, 6.23(%).

*3'-(2-Benzoyl-4-chlorophenyl)-5-chloro-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (**D03**)*

M.p**:** 218^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3201 (N-H str), 3062 (Ar C-H str), 2962 (Ali C-H Str), 1696 (C=O str), 1671 (Spiro C=O), 1607 (N-C=O str), 733 (C-S str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.07 (s, 1H), 7.76 (d, *J* =2.4 Hz, 1H), 7.71-7.69 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.48-7.36 (m, 5H), 7.32-7.30 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.19-7.18 (d, *J* =2.4 Hz, 1H), 7.0 (d, *J* =8.8 Hz, 1H), 6.86-6.84 (d, *J* =8.8 Hz, 1H), 3.769 (s, 2H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 196, 184, 174, 111-141, 78, 35; Anal. Found: C, 58.86; H, 2.91; N, 5.97; S, 6.83(%). Calc. for ($C_{23}H_{14}Cl_2N_2O_3S$): C, 58.80; H, 2.98; N, 5.96; S, 6.83 (%).

*3'-(2-Benzoyl-4-chlorophenyl)-5-nitro-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (**D04**)*

M.p**:** 211 ^{o}C**;** IR (KBr) λ_{max} in cm^{-1}: 3379 (N-H Str), 3062 (Ar C-H Str), 2924 (Ali C-H Str), 1705 (C=O str), 1663 (Spiro C=O), 1616 (N-C=O str), 732 (C-S str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.45 (s, 1H), 8.24-8.22 (dd, *J* =8.4 Hz, 2.4 Hz, 1H), 7.83-7.82 (d, *J* =2.4 Hz, 1H), 7.74-7.72 (d, *J* =8.4 Hz, 1H), 7.51-7.33 (m, 5H), 7.31-7.29 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.19-7.18 (d, *J* =2.4 Hz, 1H), 6.91-6.88 (d, *J* =8.8 Hz, 1H), 3.758 (s, 2H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 196, 182, 174, 112-144, 78, 34; Anal. Found: C, 57.51; H, 2.91; N, 8.75; S, 6.68(%). Calc. for ($C_{23}H_{14}ClN_3O_5S$): C, 57.57; H, 2.94; N, 8.76; S, 6.68(%).

*3'-[4-Chloro-2-(phenylcarbonyl)phenyl]-5'-methyl-4'H-spiro[indole-3,2'-[1,3] thiazolidine]-2, 4' (1H)-dione; (**E01**)*

M.p**:** 234 ^{o}C; IR (KBr) λ_{max} in cm^{-1}: 3209 (N-H Str), 3055 (Ar C-H Str), 2924, 2877 (Ali C-H Str), 1705 (C=O str), 1672 (Spiro C=O), 1604 (N-C=O str),728 (C-S str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.56 (s, 1H), 7.73-7.69 (t, *J* =8.4 Hz, 1H), 7.64-7.62 (d, *J* =7.6 Hz, 1H), 7.52-7.37 (m, 5H), 7.33-7.30 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.29-7.25 (d, *J* =7.6 Hz, 1H), 7.18-7.17 (d, *J* =2.4 Hz, 1H), 7.07-7.03 (t, *J* =7.6 Hz, 1H), 6.93-6.91 (d, *J* =8.8 Hz, 1H), 3.87-3.81 (q, *J* =7.2 Hz, 1H), 1.38-1.37 (d, *J* =7.2 Hz, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 196, 184, 178, 110-141, 79, 49, 19; Anal. Found: C, 64.21; H, 3.82; N, 6.24; S, 7.14 (%). Calc. for ($C_{24}H_{17}ClN_2O_3S$): C, 64.15; H, 3.78; N, 6.23; S, 7.14(%).

5-Bromo-3'-[4-chloro-2-(phenylcarbonyl)phenyl]-5'-methyl-4'H-spiro[indole-3,2'-[1,3] thiazolidine]-2,4'(1H)-dione; (E02)

M.p**:** 225 ^{o}C; IR (KBr) λ_{max} in cm^{-1}: 3417 (N-H Str), 3062 (Ar C-H Str), 2924, 2877 (Ali C-H Str), 1705 (C=O str), 1661 (Spiro C=O), 1612 (N-C=O str), 740 (C-S str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.59 (s, 1H), 7.69-7.66 (dd, *J* =8.4 Hz, 2.4 Hz,1H), 7.64-7.63 (d, *J* =2.4 Hz, 1H), 7.49-7.37 (m, 5H), 7.35-7.32 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.18-7.17 (d, *J* =2.4 Hz, 1H), 6.93-6.91 (d, *J* =8.8 Hz, 1H), 3.61-3.55 (q, *J* =7.2 Hz, 1H), 1.35-1.33 (d, *J* =7.6 Hz, 3H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 196, 184, 178, 110-141, 80, 49, 19; Anal. Found: C, 54.61; H, 3.06; N, 5.31; S, 6.07(%). Calc. for ($C_{24}H_{16}ClBrN_2O_3S$): C, 54.56; H, 3.03; N, 5.30; S, 6.07(%).

*5-Chloro-3'-[4-chloro-2-(phenylcarbonyl)phenyl]-5'-methyl-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (**E03**)*

M.p**:** 212 ^{o}C; IR (KBr) λ_{max} in cm^{-1}: 3417 (N-H Str), 3062 (Ar C-H Str), 2924, 2877 (Ali C-H Str), 1705 (C=O str), 1664 (Spiro C=O), 1612 (N-C=O str), 731 (C-S str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.05 (s, 1H), 7.64-7.61 (dd, *J* =8.4 Hz, 2.4 Hz,1H), 7.59-7.52 (d, *J* =2.4 Hz, 1H), 7.42-7.35 (m, 5H), 7.32-7.29 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.19-7.18 (d, *J* =2.4 Hz, 1H), 6.91-6.89 (d, *J* =8.8 Hz, 1H), 6.84-6.82 (d, *J* =8.8 Hz, 1H), 3.49-3.44 (q, *J* =6.8 Hz, 1H), 1.32-1.31 (d, *J* =7.6 Hz, 3H) ; ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 196, 184, 178, 111-141, 79, 49, 18; Anal. Found: C, 59.64; H, 3.34; N, 5.80; S, 6.63(%). Calc. for ($C_{24}H_{16}Cl_2N_2O_3S$): C, 59.58; H, 3.31; N, 5.79; S, 6.63(%).

*3'-[4-Chloro-2-(phenylcarbonyl)phenyl]-5'-methyl-5-nitro-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (**E04**)*

M.p**:** 236 ^{o}C; IR (KBr) λ_{max} in cm^{-1}: 3379 (N-H Str), 3062 (Ar C-H Str), 2924, 2854 (Ali C-H Str), 1705 (C=O str), 1641 (Spiro C=O), 1607 (N-C=O str), 732 (C-S str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.68 (s, 1H), 8.64-8.61 (dd, *J* =8.8 Hz, 2.4 Hz, 1H), 7.94 (d, *J* =2.4 Hz, 1H), 7.50-7.35 (m, 5H), 7.32-7.29 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.19-7.18 (d, *J* =2.4 Hz, 1H), 6.92-6.89 (d, *J* =8.8 Hz, 1H), 3.49-3.43 (q, *J* =7.2 Hz, 1H), 1.32-1.31 (d, *J* =7.6 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 196, 183, 178, 109-144, 79, 49, 19; Anal. Found: C, 58.36; H, 3.26; N, 8.51; S, 6.50(%). Calc. for ($C_{24}H_{16}ClN_3O_5S$): C, 58.31; H, 3.23; N, 8.50; S, 6.49(%).

Antimicrobial activity

In vitro antibacterial activity was determined by Kirby-Bauer disc diffusion method against bacteria such as *Staphylococcus aureus* and *Bacillus* (Gram +ve), *Salmonella typhi* and

Pseudomonas aeruginosa (Gram -ve) using *Ampicilin* as a standard drug. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 24 h incubation at 35-37 ^{o}C.

Similarly antifungal activity was performed against *Candida*. The standard and test compounds were prepared in DMSO at different concentrations. The zone of inhibition was compared with standard drug after 48 h at 25 ^{o}C. The results of antibacterial and antifungal activity are presented in Table 1.

Table 1. Antimicrobial activity of the synthesized compounds Zone of inhibition (mm) of synthesized compounds

Sample code	Anti-bacterial activity																Anti-fungal activity			
	Gram positive								Gram negative											
	Staphylococcus.spp				*Bacillus.spp*				*Salmonella.spp*				*Pseudomonas.spp*				*Candida*			
	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std	100 mcg	50 mcg	25 mcg	Std
D01	07	02	-	11	02	03	-	10	05	02	-	10	08	05	02	11	16	09	02	21
D02	06	05	03	11	08	07	06	09	08	05	02	10	05	02	-	10	07	04	02	15
D03	06	03	03	10	08	06	04	10	07	04	02	10	08	05	02	11	19	13	10	21
D04	07	06	05	11	07	06	02	09	07	05	03	09	07	04	03	11	17	11	08	21
E01	07	06	03	08	07	05	02	10	09	06	02	11	09	06	03	12	10	06	04	20
E02	09	06	04	12	10	07	03	11	07	05	02	09	08	05	02	12	10	07	03	14
E03	08	05	03	10	09	05	02	11	09	05	-	11	09	06	03	10	17	09	05	20
E04	07	04	02	11	06	02	-	12	07	04	-	10	08	04	02	11	18	10	07	21

The compounds of **D01–D04** and **E01–E04** showed significant activity against selected bacteria. Antifungal activity was performed on *candida*. The compounds **D02, E02, E03** and **D04** showed moderate activity against the fungus. The compound **D03** was more active among screened compounds against *Candida*.

Conclusion

The reaction profile explained in the present work is very efficient to synthesis, characterization and antimicrobial evaluation of 5–Br, 5-Cl and 5–NO_2 indole–2,3–dione based spiro–4–thiazolidiones. The prepared compounds showed significant and moderate antimicrobial activities and these are promising compounds for further pharmacological studies.

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