Available online at www.derpharmachemica.com

ISSN 0975-413X
CODEN (USA): PCHHAX

Der Pharma Chemica, 2016, 8(2):292-296
(http://derpharmachemica.com/archive.html)

Synthesis, characterization and antimicrobial activity of spiro-4-thiazolidione derivatives from 5-substituted indole-2,3-dione

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ABSTRACT

*In the present study, a series of 5–fluro and 5–Iodo indole–2,3–dione based spiro–4–thiazolidiones was synthesized, characterization and evaluated for their antimicrobial activity. Condensation of 5–fluro and 5–Iodo indole–2,3–dione with substituted primary aryl amine to give a Schiff bases (**A05, A06**) which on reaction with thioglycolic acid and thiolactic acid in 1,4-dioxane afforded the formation of the corresponding 4-thiazolidinones (**D05, D06, E05 and E06**). 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 (**A05, A06, D05, D06, E05 and E06**) showed significant activity against all the bacteria and fungus.*

Key words: 5–fluro & 5–Iodo indole– 2,3–dione, spiro–4–thiazolidiones, antimicrobial.

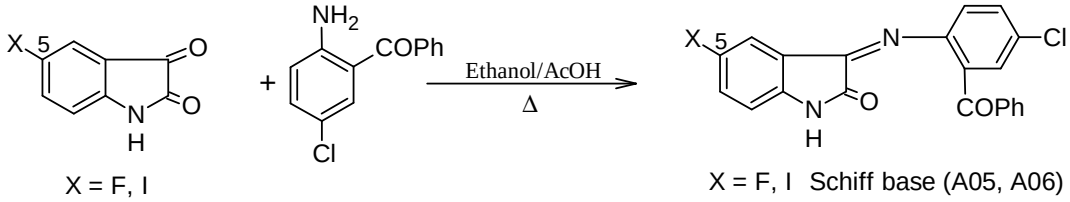
INTRODUCTION

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 [1]. It was first prepared by Erdmann and Laurent through the oxidation of indigo by nitric acid and chromic acids [2,3]. Some of its derivatives specifically Haloisatin and Nitroisatins show a wide range of biological and pharmacological activity, such as antimicrobial [4–9], anticonvulsant [10,11], analgesic [12,13], anticancer [14,15], anti-tubercular [16], antiviral [17–19], anti-HIV [20] activities. The literatures survey revealed that introduction of electron withdrawing groups at positions 5, 6 and 7 greatly increased activities from that of isatin, with substitution at the 5th position being most favorable. 4–thiazolidinones have been shown to have various important biological activities such as antibacterial, antifungal, antiviral, diuretic, antituberculostatic, anti-HIV, antihistaminic, anticancer, anticonvulsant, antiinflammatory and analgesic properties [21–23]. Spirocyclic systems containing one carbon atom common to two rings are structurally interesting [24]. Spiro compounds represent an important class of naturally occurring substances and their characteristic is the highly biological properties [25,26]. Spiro heterocyclic compounds including thiazolidine moiety have antimicrobial activity[27]. Spiro-indole heterocyclic, in which the indole ring is linked to the other heterocyclic system through the spirocarbon atom at C-3, shows an increased spectrum of biological activities. In view of these data have been undertaken the synthesis, characterization and antimicrobial evaluation of 5–fluro and 5–Iodo indole–2,3–dione based spiro–4–thiazolidiones. 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. The physical data of titled compounds are summarized and present in the result and discussion part.

MATERIALS AND METHODS

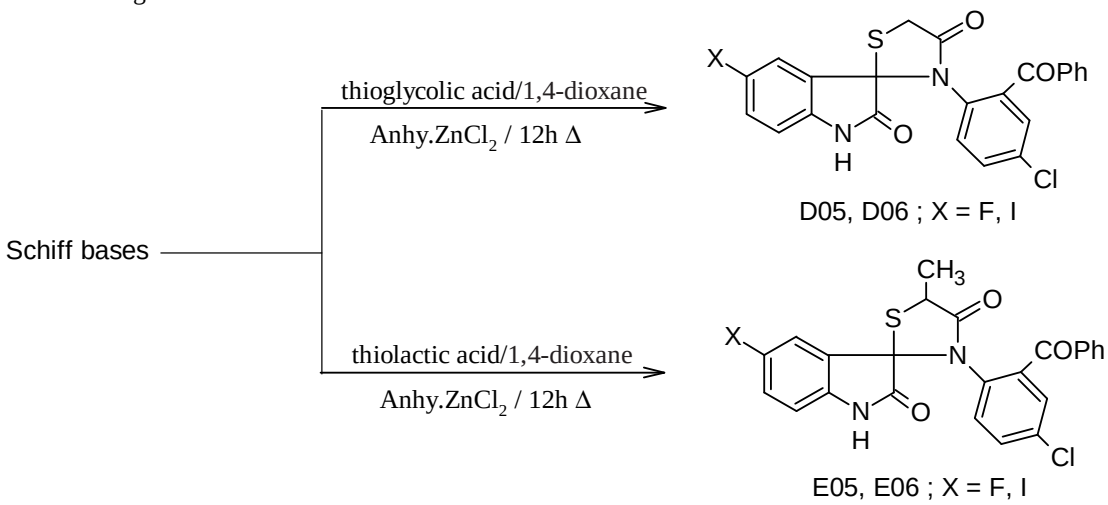
The melting points were carried out in open capillary tube and were uncorrected. Thin layer chromatography was performed using silica gel coated on a glass plate and spots were visualized by exposure to iodine vapour. IR spectra of compounds were scanned on Shimadzu IR spectrophotometer using KBr disc and expressed in cm^{-1}. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-D_6 on BRUKER (400MHz) spectrometer using TMS as an internal standard (chemical shifts in δ, ppm). The elemental analysis for C, H, and N were in an agreement with the calculated values. The synthesis of the target compounds was accomplished according to the reaction sequence illustrated in Scheme 1 and Scheme 2.



Scheme 1

(1) General method for Synthesis schiff base [29] **(A05 & A06)**

A equimolar (0.01 mole) mixture of 2–amino–5–chlorobenzophenone and 5–substituted indole– 2,3–dione were dissolved in 20mL of ethanol with few drops of acetic acid. It is reacted under refluxing conditions. After the completion of reaction the content was cooled and kept an overnight. The separated product was filtered and recrystallized using ethanol.



Scheme 2

(2) Synthesis of 5–substituted indol–2,3–dione based spiro–4–thiazolidiones* [**30] ***(D05 & D06)

A mixture of Schiff bases (A05) (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 **D05**. Similarly other compound of **D06** was synthesized from A06 by the same procedure.

(3) Synthesis of 5–substituted indol–2,3–dione based 5'–methyl–spiro–4–thiazolidiones **[**30] ***(E05 & E06)***
A mixture of Schiff bases (A05) (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 **E05**. Similarly other compound of **E06** was synthesized from A06 by the same procedure.

RESULTS AND DISCUSSION

Synthesis of Schiff base was obtained by above the scheme 1 and Synthesis of 4–thiazolidiones was obtained by above the scheme 2. The required starting material Schiff base **(A05, A06)** was synthesed from 5–substituted indole–2,3–dione which were further on treatment with thioglycolic acid and thiolactic acid yielded the 4-thiazolidinones **(D05, D06, E05 & E06)**. The spectral analysis of the compounds were done by IR, ^{1}H and ^{13}C NMR and the spectral data were consistent with the assigned structures.

3-[(2-benzoyl-4-chlorophenyl)imino]-5-fluoro-1,3-dihydro-2H-indol-2-one; (A05):
m.p**:** 196^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3417 (N-H Str), 2924 (Ar C-H Str), 1735 (C=O str), 1612 (N-C=O str), 1573 (imino C=N); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 11.03 (s, 1H), 7.61 – 7.58 (dd, *J* =8.8 Hz, 2.4 Hz, 1H), 7.55 (d, *J* =2.4 Hz, 1H), 7.49 – 7.33 (m, 5H), 7.32 – 7.29 (dd, *J* = 8.7 Hz, 2.4 Hz, 1H), 7.18 – 7.17 (d, *J* =2.4 Hz, 1H), 6.95 – 6.93 (d, *J* =8.8 Hz, 1H), 6.91 – 6.89 (d, *J* =8.8 Hz, 1H); ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 196, 183, 156, 109–156; Anal. Found: C, 64.96; H, 3.07; N, 7.21 (%). Calc. for ($C_{21}H_{12}ClFN_2O_2$): C, 64.98; H, 3.09; N, 7.22 (%).

3-[(2-benzoyl-4-chlorophenyl)imino]-5-iodo-1,3-dihydro-2H-indol-2-one; (A06):
m.p**:** 201^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3417 (N-H Str), 3092 (Ar C-H Str), 1735 (C=O str), 1612 (N-C=O str), 1573 (imino C=N); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 11.10 (s, 1H), 7.76 – 7.75 (d, *J* =2.4 Hz, 1H), 7.62 – 7.60 (dd, *J* =8.8 Hz, 2.4 Hz, 1H), 7.51 – 7.37 (m, 5H), 7.33 – 7.31 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.18 (d, *J* =2.4 Hz, 1H), 6.91 – 6.89 (d, *J* =8.8 Hz, 1H), 6.77 – 6.75 (d, *J* =8.4 Hz, 1H); ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 196, 183, 158, 114–146, 90; Anal. Found: C, 51.76; H, 2.47; N, 5.76 (%). Calc. for ($C_{21}H_{12}ClIN_2O_2$): C, 51.77; H, 2.46; N, 5.75 (%).

3'-(2-benzoyl-4-chlorophenyl)-5-fluro-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (D05): m.p**:** 189^{0}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), 1673 (Spiro C=O), 1612 (N-C=O str), 732 (C-S str); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 11.65 (s, 1H), 7.62 – 7.59 (dd, *J* =8.4 Hz, 2.4 Hz, 1H), 7.56 (d, *J* =2.4 Hz, 1H), 7.50 – 7.37 (m, 5H), 7.34 – 7.32 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.19 – 7.18 (d, *J* =2.4 Hz, 1H), 6.94 – 6.92 (d, *J* =8.8 Hz, 1H), 6.90 – 6.88 (d, *J* =8.8 Hz, 1H), 3.73 (s, 2H); ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 196, 184, 174, 110–140, 78, 34; Anal. Found: C, 60.01; H, 3.12; N, 6.19; S, 7.08 (%). Calc. for ($C_{23}H_{14}ClFN_2O_3S$): C, 60.94; H, 3.09; N, 6.18; S, 7.07 (%).

3'-(2-benzoyl-4-chlorophenyl)-5-iodo-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (D06): m.p**:** 209^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3417 (N-H str), 3062 (Ar C-H str), 2924 (Ali C-H Str), 1733 (C=O str), 1680 (Spiro C=O), 1612 (N-C=O str), 732 (C-S str); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 11.12 (s, 1H), 7.77 (d, *J* =2.4 Hz, 1H), 7.68 – 7.65 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.54 – 7.37 (m, 5H), 7.34 – 7.32 (dd, *J* = 8.8 Hz, 2.4 Hz, 1H), 7.19 – 7.18 (d, *J* =2.4 Hz, 1H), 6.92 – 6.90 (d, *J* =8.8 Hz, 1H), 6.77 – 6.75 (d, *J* =8.8 Hz, 1H), 3.76 (s, 2H); ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 196, 183, 174, 112–142, 91, 78, 34; Anal. Found: C, 49.26; H, 2.52; N, 5.01; S, 5.72 (%). Calc. for ($C_{23}H_{14}ClIN_2O_3S$): C, 49.21; H, 2.49; N, 4.99; S, 5.71 (%).

5-Fluro-3'-[4-chloro-2-(phenylcarbonyl)phenyl]-5'-methyl-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (E05): m.p**:** 210^{0}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), 1652 (Spiro C=O), 1620 (N-C=O str), 736 (C-S str); ^{1}H-NMR (DMSO-d$_6$, 400 MHz) δ: 11.59 (s, 1H), 7.63 – 7.60 (dd, *J* =8.8 Hz, 2.4 Hz,1H), 7.59 – 7.58 (d, *J* =2.4 Hz, 1H), 7.52 – 7.37 (m, 5H), 7.32 – 7.29 (dd, *J* = 9.2 Hz, 2.4 Hz, 1H), 7.19 (d, *J* =2.4 Hz, 1H), 6.97 – 6.95 (d, *J* =8.8 Hz, 1H), 6.92 – 6.89 (d, *J* =8.8 Hz, 1H), 3.58 – 3.53 (q, *J* =7.6 Hz, 1H), 1.35 – 1.34 (d, *J* =6.8 Hz, 3H) ; ^{13}C-NMR (DMSO-d$_6$, 100 MHz) δ: 196, 184, 178, 162, 109–140, 80, 48, 19; Anal. Found: C, 61.74; H, 3.45; N, 6.01; S, 6.78 (%). Calc. for ($C_{24}H_{16}ClFN_2O_3S$): C, 61.68; H, 3.42; N, 5.99; S, 6.86 (%).

5-Iodo-3'-[4-chloro-2-(phenylcarbonyl)phenyl]-5'-methyl-4'H-spiro[indole-3,2'-[1,3]thiazolidine]-2,4'(1H)-dione; (E06): m.p**:** 213^{0}C**;** IR (KBr) λ_{max} in cm^{-1}: 3224 (N-H Str), 3062 (Ar C-H Str), 2924, 2854 (Ali C-H Str),

1697 (C=O str), 1672 (Spiro C=O), 1597 (N-C=O str), 732 (C-S str); ^{1}H-NMR (DMSO-d_6, 400 MHz) δ: 11.12 (s, 1H), 7.76 (d, *J* =2.4 Hz, 1H), 7.68 – 7.66 (dd, *J* =8.8 Hz, 2.4 Hz, 1H), 7.52 – 7.34 (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), 6.92 – 6.90 (d, *J* =8.8 Hz, 1H), 3.57 – 3.41 (q, *J* =7.2 Hz, 1H), 1.60 – 1.58 (d, *J* =6.8 Hz, 1H); ^{13}C-NMR (DMSO-d_6, 100 MHz) δ: 196, 183, 178, 142–112, 91, 79, 49, 19; Anal. Found: C, 50.15; H, 2.81; N, 4.87; S, 5.58 (%). Calc. for ($C_{24}H_{16}ClIN_2O_3S$): C, 50.10; H, 2.78; N, 4.87; S, 5.57 (%).

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 standard 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 hrs incubation at 35-37^{0}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 hrs at 25^{0}C.

The results of antibacterial and antifungal activity are presented in Table 1.

The compounds of A05, A06, D05, D06, E05 & E06 showed significant activity against selected bacteria. Antifungal activity was performed on *Candida*. All the compounds showed moderate activity against the fungus. The compound D05 was more active among screened compounds.

Table1. 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
A05	08	05	04	10	07	05	03	12	08	05	03	11	08	06	03	10	16	09	02	21
A06	06	05	03	10	08	04	02	11	06	02	-	08	05	03	-	08	10	04	02	15
D05	09	06	03	11	06	05	02	10	08	04	02	11	08	04	-	11	19	10	08	21
D06	06	05	04	11	07	04	02	09	07	04	-	09	07	04	03	10	17	09	04	21
E05	06	05	03	09	08	05	03	10	09	06	02	10	09	05	02	12	15	07	06	20
E06	08	05	03	11	09	07	03	11	07	04	02	08	08	04	-	11	13	07	05	18

CONCLUSION

The reaction profile explained in the present work is very efficient to synthesis, characterization and antimicrobial evaluation of 5–fluro and 5–Iodo 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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