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Synthesis and pharmacological studies of some phthalimidoxy substituted spiro-thiazolidinone derivatives of isatin

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Novel spiro-isatin-thiazolidino-pyrazoline compounds containing alkoxyphthalimide moiety have been synthesized through a four step pathway starting from chalcone **1a-e**. Cyclization of these with hydrazine hydrate in absolute ethanol have yielded 1-acetyl-3-(4-aminophenyl)-5-(4-substituted phenyl)-2-pyrazoline **2a-e**. Acid catalyzed condensation of **2a-e** with isatin **3** has yielded 3-[4-{1-acetyl-5-(4-substituted phenyl)-2-pyrazoline-3-yl}phenylimino]indole-2-one **4a-e**. These Schiff bases on reaction with mercaptoacetic acid in presence of anhydrous $ZnCl_2$ gave their corresponding spiro-thiazolidinone derivatives **5a-e**. Subsequent treatment with bromoethoxyphthalimide yielded titled compounds 3'-{4-(1-acetyl-5-(4-substituted phenyl)-2-pyrazoline-3-yl)phenyl}-1-*N*-ethoxyphthalimido-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-dione **6a-e**.

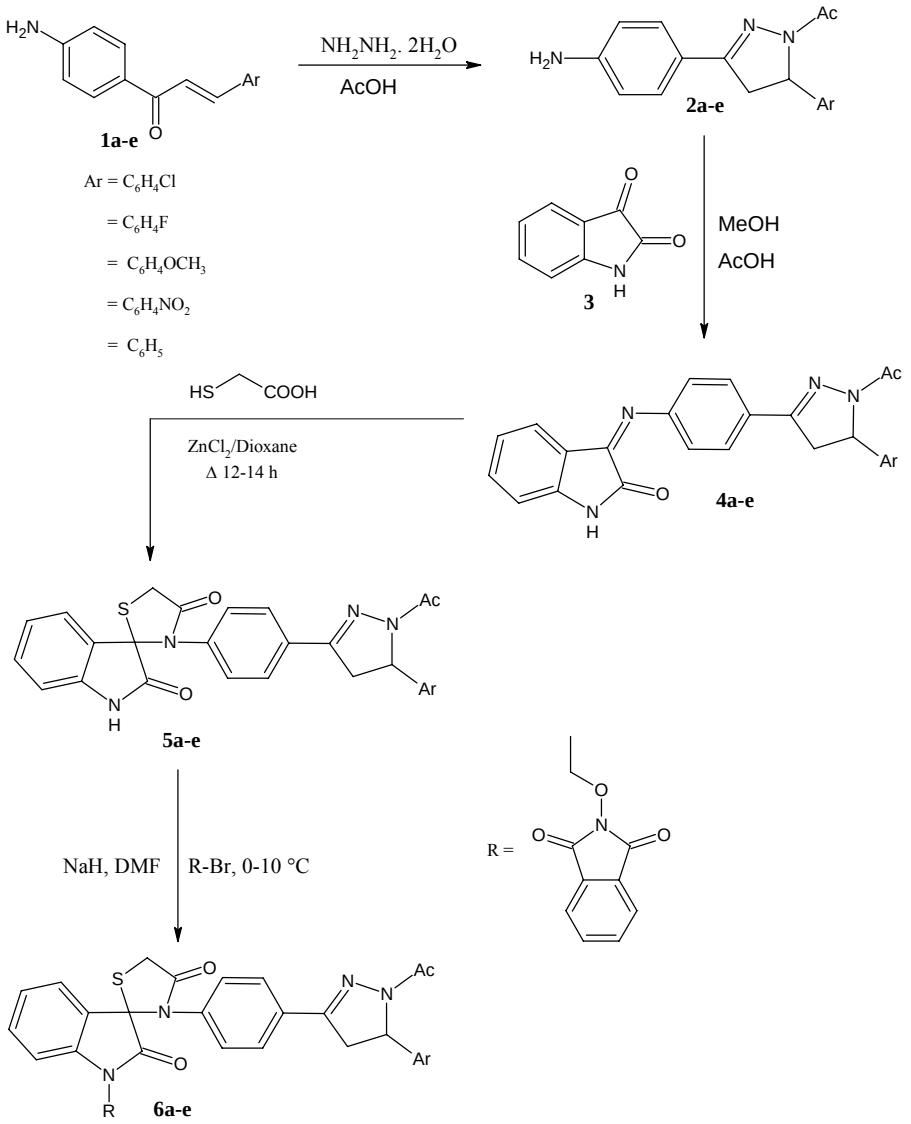
Keywords: Pyrazoline, isatin, spiro-thiazolidinone, bromoethoxyphthalimide

Pyrazoline derivatives have been studied extensively because of their ready accessibility, diverse chemical reactivity and extensive biological activity. The pharmaceutical importance of various substituted pyrazolines lies in the fact that these can be effectively utilized as antibacterial[1], antitubercular[2] and insecticidal agents[3]. Some of these compounds have manifested substantial antidiabetic[4] and analgesic properties[5]. The chemical versatility of isatin (2,3-indolinone) derivatives has led to their extensive use as synthons for the preparation of many biologically active compounds[6,7]. Isatin is an endogenous compound identified in humans that possesses wide range of biological activities. Isatin has anxiogenic[8] activity and acts as a potent antagonist on atrial natriuretic peptide receptors *in vitro*[9]. Isatin-derived compounds possess a wide spectrum of medicinal properties and have been studied for activity against tuberculosis[10], trypanosomiasis[11] and as anticonvulsants[12] . Spiro derivatives of isatin have attracted the attention of chemists in view of their analgesic[13] and antiphologistic[14] activities and their use as a blood platlet aggregators[15]. Moreover, thiazolidinones have a broad spectrum of pharmacological properties *viz*. anti-HIV[16], antifungal[17], antipsychotic[18], anticonvulsant[19] etc. Several derivatives of alkoxyphthalimide have been already synthesized[20,21] and reported to demonstrate a wide range of pharmacological activities like antimalarial[22], antiepileptic[23], anticonvulsant[24] etc.

In view of above mentioned facts and in connection with earlier work on the synthesis of ethoxyphthalimide derivatives of heterocycles, it appeared expedient to synthesize 3'-{4-(1-acetyl-5-(4-substituted phenyl)-2-pyrazoline-3-yl)phenyl}-1-*N*-ethoxyphthalimido-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-dione **6a-e** *via* a series of reactions. **(Scheme I, Table I)**.

Result and Discussion

An efficient and convenient synthesis of ethoxyphthalimide derivative of some pyrazolo-spiro-indole-thiazolidinones through a multistep process had been carried out. For this purpose, chalcone **1a-e** was allowed to react with hydrazine hydrate to give 1-acetyl-3-(4-aminophenyl)-5-aryl-2-pyrazoline **2a-e**. The appearance of C=N band at 1632 cm^{-1} and no absorption in the region 1678 cm^{-1} clearly indicated that –CO-CH=CH- moiety of chalcone underwent cyclization to a pyrazoline ring in **2a-e**. The structure was further supported by its ^1H NMR spectra which



Scheme I

exhibited three double doublets due to presence of two diastereotopic protons at C_4 and one single proton at C_5 which appeared in the region δ 3.01, 4.19 and 5.30 respectively. Appearance of a singlet at δ 3.43 due to methyl group of $COCH_3$, further confirmed the structure of **2a.** Acid catalyzed condensation of **2a-e** with isatin **3** was carried out to afford corresponding 3-[4-{1-acetyl-5-aryl-2-pyrazolin-3-yl}-phenylimino]-indol-2-one **4a-e**. The IR spectra of compounds **4a-e** were characterized by absence of absorption band at 3494-3333 cm^{-1} which was present in its precursor. Compounds **4a-e** on refluxing with mercaptoacetic acid in DMF for 8-10 hr in the presence of catalytic amount of anhy. $ZnCl_2$ afforded 3'-{4-(1-acetyl-5-(4-substituted phenyl)-2-pyrazoline-3-yl)phenyl}-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-diones **5a-e**. Formation of compounds **5a-e** was confirmed by appearance of peak at 1710 cm^{-1}, which was due to >C=O group of thiazolidinone ring. Appearance of new singlet at δ 3.32 due to S-CH_2 group, also confirmed its formation. When bromoethoxyphthalimide was condensed with **5a-e** in NaH and DMF, formation of 3'-{4-(1-acetyl-5-(4-substitutedphenyl)-2-pyrazoline-3-yl)phenyl}-1-*N*-ethoxy-phthalimido-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-dione **6a-e** was achieved. Two characterstic triplets of O-CH_2 and N-CH_2 at δ 4.33 and 2.93 respectively in ^{1}H NMR spectra, C-H stretching vibration band in IR spectra and molecular ion peak in mass spectra proved the structure.

Table I — Physical and analytical data of synthesized compounds

Compd	Mol. formula	Mol. Weight	Ar	m.p. (°C)	Yield (%)	Found/Calcd (%) C	Found/Calcd (%) N
2a	$C_{17}H_{16}ClN_3O$	313	C_6H_4Cl	140	68	65.02 (65.07	13.27 13.39)
2b	$C_{17}H_{16}FN_3O$	297	C_6H_4F	172	72	68.58 (68.67	14.11 14.13)
2c	$C_{18}H_{19}N_3O_2$	309	$C_6H_4OCH_3$	164	69	69.81 (69.88	13.55 13.59)
2d	$C_{17}H_{16}N_3O_2$	324	$C_6H_4NO_2$	210	62	62.84 (62.95	17.05 17.28)
2e	$C_{17}H_{17}N_3O$	279	C_6H_5	156	70	73.03 (73.10	15.00 15.05)
4a	$C_{25}H_{19}ClN_4O_2$	442	C_6H_4Cl	186	66	67.72 (67.80	12.60 12.65)
4b	$C_{25}H_{19}FN_4O_2$	426	C_6H_4F	190	69	70.32 (70.41	13.09 13.14)
4c	$C_{26}H_{22}N_4O_3$	438	$C_6H_4OCH_3$	202	71	71.16 (71.22	12.75 12.78)
4d	$C_{25}H_{19}N_5O_4$	453	$C_6H_4NO_2$	278	63	66.13 (66.22	15.39 15.45)
4e	$C_{25}H_{20}N_4O_2$	408	C_6H_5	204	68	73.45 (73.51	13.69 13.72)
5a	$C_{27}H_{21}ClN_4O_3S$	516	C_6H_4Cl	233	70	62.65 (62.73	10.81 10.84)
5b	$C_{27}H_{21}FN_4O_3S$	500	C_6H_4F	202	68	64.69 (64.79	11.08 11.20)
5c	$C_{28}H_{24}N_4O_4S$	512	$C_6H_4OCH_3$	261	63	65.53 (65.61	10.89 10.93)
5d	$C_{27}H_{21}N_5O_5S$	527	$C_6H_4NO_2$	321	60	61.39 (61.47	13.23 13.28)
5e	$C_{27}H_{22}N_4O_3S$	482	C_6H_5	197	64	67.12 (67.20	11.55 11.61)
6a	$C_{37}H_{28}ClN_5O_6S$	705	C_6H_4Cl	123	64	62.77 (62.85	9.88 9.92)
6b	$C_{37}H_{28}FN_5O_6S$	689	C_6H_4F	132	67	64.81 (64.92	10.03 10.15)
6c	$C_{38}H_{31}N_5O_7S$	701	$C_6H_4OCH_3$	141	57	65.66 (65.74	9.91 9.98)
6d	$C_{37}H_{28}N_6O_8S$	716	$C_6H_4NO_2$	163	60	61.51 (61.59	11.69 11.73)
6e	$C_{37}H_{29}N_5O_6S$	671	C_6H_5	113	66	67.27 (67.34	10.38 10.43)

Antimicrobial Activity

Five synthesized compounds **6a-e** were *in vitro* screened for their antibacterial and antifungal activity using 100 µg/mL concentrations in DMF by cup and well method[25]. The micro-organisms *Proteus mirabilis*, *Bacillus subtilis*, *Klebsiella pneumoniae*, *Escherichia coli* were used as antibacterials, *Candida albicans* and *Aspergillus fumigatus* were used as

fungal strains. The activity is presented as zone of inhibition in mm and compared with activity of controls C_1 and C_2 (for antibacterial activity C_1= ciprofloxacin, C_2= roxithromycin and for antifungal activity C_1= amphotericin and C_2= flucanazole) to give activity index value **(Table II)**.

All the compounds showed poor activity against *K. pneumoniae* and *E. coli* where as moderate to strong activity was shown against *P. mirabilis* and *B. subtilis*. Activity index value against *P. mirabilis* and *B. subtilis* was more than one for majority of compounds. It was interesting to note that all the compounds showed stronger activity than the standard used against *Candida albicans* and *Aspergillus fumigatus.*

It was concluded from the activity study that compound **6b** was found to be the strongest amongst all synthesized compounds. Compounds under study showed more comprehensive fungus-inhibiting properties than that of the bacterial. Even two folds antifungal activity was observed for these compared to standard. As far as the relation between structure and activity are concerned the chloro, fluoro and nitro substituted compounds were found to have better activity than the others.

Experimental Section

Melting points were taken in open capillary tubes and are therefore uncorrected. Purity of the compounds was checked on silica gel G TLC plates of 2 mm thickness using *n*-hexane and ethylacetate as solvent system. The visualization of spot was carried out in an iodine chamber. The IR spectra were recorded on a Perkin-Elmer spectrometer. The ^{1}H NMR spectra were scanned on a Bruker DRX-300 MHz. spectrometer (300 MHz) in $CDCl_3$ using TMS as internal standard and chemical shifts are expressed in δ ppm. The mass spectra were recorded on a Jeol SX-102 (FAB) spectrometer. Phthalimidoxyethyl bromide[26] and 1-(4-aminophenyl)-3-(substituted phenyl)-prop-2-en-1-one[27] (chalcone) **1a-e** were synthesized by literature method. The physical and analytical data of synthesized compounds are presented in **Table I.**

Synthesis of 1-acetyl-3-(4-aminophenyl)-5-(4-chlorophenyl)-2-pyrazoline 2a: A mixture of chalcone **1a** (0.01 mole) and hydrazine hydrate (0.013 mole) in absolute ethanol (20 mL) in the presence of catalytic amount (3-4 drops) of gl. acetic acid was kept under reflux for 6-8 hr. The solution was concentrated by distillation under reduced pressure and after cooling solid obtained was filtered off, washed with water, dried and crystallized from ethanol.

Table II — Antimicrobial activity of the synthesized compounds **6a-e**

Compound	Antibacterial Activity				Antifungal Activity	
	P. mirabilis	*B. subtilis*	*K. pneumoniae*	*E.coli*	*C. albicans*	*A. fumigatus*
6a	13 (0.92)^{C_1} (1.3)^{C_2}	10 (0.90)^{C_1} (1.66)^{C_2}	5 (0.41)^{C_1} (0.83)^{C_2}	5 (0.41)^{C_1} (0.50)^{C_2}	12 (1.00)^{C_1} (2.00)^{C_2}	6 (1.00)^{C_1} (2.00)^{C_2}
6b	15 (1.07)^{C_1} (1.50)^{C_2}	11 (1.00)^{C_1} (1.83)^{C_2}	4 (0.33)^{C_1} (0.66)^{C_2}	7 (0.58)^{C_1} (0.70)^{C_2}	13 (1.08)^{C_1} (2.16)^{C_2}	8 (1.33)^{C_1} (2.66)^{C_2}
6c	9 (0.64)^{C_1} (0.90)^{C_2}	8 (0.72)^{C_1} (1.33)^{C_2}	3 (0.25)^{C_1} (0.50)^{C_2}	NA	9 (0.75)^{C_1} (1.50)^{C_2}	5 (0.83)^{C_1} (1.66)^{C_2}
6d	12 (0.85)^{C_1} (1.20)^{C_2}	10 (0.90)^{C_1} (1.66)^{C_2}	4 (0.33)^{C_1} (0.66)^{C_2}	5 (0.41)^{C_1} (0.50)^{C_2}	11 (0.91)^{C_1} (1.83)^{C_2}	7 (1.16)^{C_1} (2.33)^{C_2}
6e	10 (0.71)^{C_1} (1.00)^{C_2}	9 (0.81)^{C_1} (1.50)^{C_2}	NA	4 (0.33)^{C_1} (0.40)^{C_2}	7 (0.58)^{C_1} (1.16)^{C_2}	5 (0.83)^{C_1} (1.66)^{C_2}
C_1	14	11	12	12	12	6
C_2	10	6	6	10	6	3

Zone of inhibition (mm) (activity index)$^{std.}$
(Activity index) = Inhibition zone of compound/Inhibition zone of the standard drug.
For antibacterial activity: C_1 = ciprofloxacin, C_2 = roxithromycin
For antifungal activity: C_1 = amphotericin B, C_2 = flucanazole
NA = Nil Activity

IR (KBr, cm^{-1}): 3494, 3333 (N-H str.), 3012 (C-H str., Ar-H), 2832 (C-H str., CH_3), 1700 (C=O str.), 1632 (C=N str.), 776 (C-Cl str.); ^1H NMR ($CDCl_3$, δ) : 7.85-7.26 (m, 8H, Ar-H), 6.77 (s, 2H, NH_2), 5.51 (dd, 1H, CH-Ar, J_1 = 6.4, J_2 = 12.7 Hz), 4.40 (dd, 1H, CHbH, J_1 = 16.5, J_2 = 12.7 Hz), 3.43 (s, 3H, $COCH_3$), 3.25 (dd, 1H, CHHa, J_1 = 16.5, J_2 = 6.4 Hz).

Compounds **2b-e** were also synthesized by the similar method using appropriate reactants with required change in reflux time.

1-Acetyl-3-(4-aminophenyl)-5-(4-fluorophenyl)-2-pyrazoline 2b: IR (KBr, cm^{-1}): 3452, 3310 (N-H str.), 3080 (C-H str., Ar-H), 2836 (C-H str., CH_3), 1685 (C=O str.), 1615 (C=N str.), 1150 (C-F str.); ^1H NMR ($CDCl_3$, δ) : 7.83-7.25 (m, 8H, Ar-H), 6.73 (s, 2H, NH_2), 5.50 (dd, 1H, CHAr, J_1 = 6.4, J_2 = 12.7 Hz), 4.42 (dd, 1H, CHbH, J_1 = 16.5, J_2 = 12.7 Hz), 3.46 (s, 3H, $COCH_3$), 3.28 (dd, 1H, CHHa, J_1 = 16.5, J_2 = 6.4 Hz).

1-Acetyl-3-(4-aminophenyl)-5-(4-methoxyphenyl)-2-pyrazoline 2c: IR (KBr, cm^{-1}): 3458, 3326 (N-H str.), 3024 (C-H str., Ar-H), 2839 (C-H str., CH_3), 1690 (C=O str.), 1617 (C=N str.), 1052 (C-O str.); ^1H NMR ($CDCl_3$, δ) : 7.87-7.31 (m, 8H, Ar-H), 6.74 (s, 2H, NH_2), 5.56 (dd, 1H, CH-Ar, J_1 = 6.4, J_2 = 12.7 Hz), 4.44 (dd, 1H, CHbH, J_1 = 16.5, J_2 = 12.7 Hz), 3.40 (s, 3H, $COCH_3$), 3.21 (dd, 1H, CHHa, J_1 = 16.5, J_2 = 6.4 Hz).

1-Acetyl-3-(4-aminophenyl)-5-(4-nitrophenyl)-2-pyrazoline 2d: IR (KBr, cm^{-1}): 3446, 3321 (N-H str.), 3011 (C-H str., Ar-H), 2830 (C-H str., CH_3), 1694 (C=O str.), 1630 (C=N str.), 1521, 1354 (NO_2 asymm. and symm. str.); ^1H NMR ($CDCl_3$, δ) : 7.97-7.30 (m, 8H, Ar-H), 6.75 (s, 2H, NH_2), 5.51 (dd, 1H, CH-Ar, J_1 = 6.4, J_2 = 12.7 Hz), 4.46 (dd, 1H, CHbH, J_1 = 16.5, J_2 = 12.7 Hz), 3.42 (s, 3H, $COCH_3$), 3.23 (dd, 1H, CHHa, J_1 = 16.5, J_2 = 6.4 Hz).

1-Acetyl-3-(4-aminophenyl)-5-phenyl-2-pyrazoline 2e: IR (KBr, cm^{-1}): 3442, 3317 (N-H str.), 3013 (C-H str., Ar-H), 2824 (C-H str., CH_3), 1696 (C=O str.), 1638 (C=N str.); ^1H NMR ($CDCl_3$, δ): 7.97-7.28 (m, 9H, Ar-H), 6.70 (s, 2H, NH_2), 5.50 (dd, 1H, CH-Ar, J_1 = 6.4, J_2 = 12.7 Hz), 4.44 (dd, 1H, CHbH, J_1 = 16.5, J_2 = 12.7 Hz), 3.40 (s, 3H, $COCH_3$), 3.22 (dd, 1H, CHHa, J_1 = 16.5, J_2 = 6.4 Hz).

Synthesis of 3-[4-{1-acetyl-5-(chlorophenyl)-2-pyrazolin-3-yl}phenylimino]indol-2-one 4a: An equimolar mixture of **2a** and isatin **3** was refluxed in methanol (40 mL) in the presence of catalytic amount (3-4 drops) of gl. acetic acid for 3 hr and allowed to cool at R T. The Schiff base thus obtained was filtered and recrystallized from methanol.

IR (KBr, cm^{-1}): 3217 (N-H str.), 3017 (C-H str., Ar-H), 2875 (C-H str., CH_3), 1700 (C=O str.), 1645 (C=N str.), 745 (C-Cl str.); ^1H NMR ($CDCl_3$, δ): 12.17 (s, 1H, NH), 7.10-6.70 (m, 12H, Ar-H), 5.32 (dd, 1H, CHAr, J_1 = 6.8, J_2 = 12.9 Hz), 4.10 (dd, 1H, CHbH, J_1 = 16.3, J_2 = 12.9 Hz), 3.34 (s, 3H, $COCH_3$), 3.20 (dd, 1H, CHHa, J_1 = 16.3, J_2 = 6.8 Hz).

Compounds **4b-e** were also synthesized by the similar method using appropriate reactants and minor modification in reaction conditions.

3-[4-{1-Acetyl-5-(fluorophenyl)-2-pyrazolin-3-yl}-phenylimino]indol-2-one 4b: IR (KBr, cm^{-1}): 3232 (N-H str.), 3031(C-H str., Ar-H), 2870 (C-H str., CH_3), 1708 (C=O str.), 1637 (C=N str.), 1175 (C-F str.); ^1H NMR ($CDCl_3$, δ) : 12.20 (s, 1H, NH), 7.43-6.82 (m, 12H, Ar-H), 5.30 (dd, 1H, CHAr, J_1 = 6.8, J_2 = 12.9 Hz), 4.17 (dd, 1H, CHbH, J_1 = 16.3, J_2 = 12.9 Hz), 3.40 (s, 3H, $COCH_3$), 3.23 (dd, 1H, CHHa, J_1 = 16.3, J_2 = 6.8 Hz).

3-[4-{1-Acetyl-5-(methoxyphenyl)-2-pyrazolin-3-yl}phenylimino]indol-2-one 4c: IR (KBr, cm^{-1}): 3223 (N-H str.), 3027 (C-H str., Ar-H), 2873 (C-H str., CH_3), 1698 (C=O str.), 1638 (C=N str.), 1090 (C-O str.); ^1H NMR ($CDCl_3$, δ): 12.12 (s, 1H, NH), 7.43-6.90 (m, 12H, Ar-H), 5.27 (dd, 1H, CHAr, J_1 = 6.8, J_2 = 12.9 Hz), 4.11 (dd, 1H, CHbH, J_1 = 16.3, J_2 = 12.9 Hz), 3.89 (s, 3H,OCH_3), 3.30 (s, 3H, $COCH_3$), 3.18 (dd, 1H, CHHa, J_1 = 16.3, J_2 = 6.8 Hz).

3-[4-{1-Acetyl-5-(nitrophenyl)-2-pyrazolin-3-yl}-phenylimino]indol-2-one 4d: IR (KBr, cm^{-1}): 3242 (N-H str.), 3022 (C-H str., Ar-H), 2870 (C-H str., CH_3), 1696 (C=O str.), 1631 (C=N str.), 1517, 1345 (NO_2 asymm. and symm. str.); ^1H NMR ($CDCl_3$, δ): 12.18 (s, 1H, NH), 7.77-6.76 (m, 12H, Ar-H), 5.28 (dd, 1H, CHAr, J_1 = 6.8, J_2 = 12.9 Hz), 4.14 (dd, 1H, CHbH, J_1 = 16.3, J_2 = 12.9 Hz), 3.46 (s, 3H, $COCH_3$), 3.21 (dd, 1H, CHHa, J_1 = 16.3, J_2 = 6.8 Hz).

3-[4-{1-Acetyl-5-phenyl-2-pyrazolin-3-yl}phenyl-imino]indol-2-one 4e: IR (KBr, cm^{-1}): 3229 (N-H str.), 3024 (C-H str., Ar-H), 2871 (C-H str., CH_3), 1702 (C=O str.), 1633 (C=N str.); ^1H NMR ($CDCl_3$, δ): 12.14 (s, 1H, NH), 7.73-6.69 (m, 13H, Ar-H), 5.30 (dd, 1H, CHAr, J_1 = 6.8, J_2 = 12.9 Hz), 4.10 (dd, 1H, CHbH, J_1 = 16.3, J_2 = 12.9 Hz), 3.38 (s, 3H, $COCH_3$), 3.27 (dd, 1H, CHHa, J_1 = 16.3, J_2 = 6.8 Hz).

Synthesis of 3'-{4-(1-acetyl-5-(4-chlorophenyl)-2-pyrazoline-3-yl)phenyl}-4'*H*-spiro[indole-3,2'-[1,3]-thiazolidene]-2,4'-1*H*-diones 5a: A well stirred

solution of **4a** (0.01 mole) in dry DMF containing pinch of anhydrous $ZnCl_2$ and thioglycolic acid (0.02 mole) was refluxed for 8 hr. Excess of solvent was distilled off and the residual reaction-mixture was cooled and poured into ice-cold water. The separated solid was filtered, washed and recrystallized from ethanol.

IR (KBr, cm^{-1}): 3310 (N-H str.), 3070 (C-H str., Ar-H), 2985 (C-H str., CH_3), 1705, 1680 (C=O str.), 1632 (C=N str.), 750 (C-Cl str.), 700 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ) : 12.11 (s, 1H, isatin NH), 7.81-6.91 (m, 12H, Ar-H), 5.52 (dd, 1H, CH-Ar, J_1 = 5.7, J_2 = 11.3 Hz), 4.43 (dd, 1H, CHbH, J_1 = 17.8, J_2 = 11.3 Hz), 4.10 (s, 2H, CH_2), 3.64 (dd, 1H, CHHa, J_1 = 17.8, J_2 = 5.7 Hz), 3.11 (s, 3H, $COCH_3$).

Compounds **5b-e** were also synthesized by the similar method using appropriate reactants with required change in reflux time.

3'-{4-(1-Acetyl-5-(4-fluorophenyl)-2-pyrazoline-3-yl)phenyl}-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-diones 5b: IR (KBr, cm^{-1}): 3302 (N-H str.), 3080 (C-H str., Ar-H), 2976 (C-H str., CH_3), 1702, 1688 (C=O str.), 1627 (C=N str.), 1150 (C-F str.), 695 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ) : 11.92 (s, 1H, isatin NH), 7.68-6.89 (m, 12H, Ar-H), 5.49 (dd, 1H, CH-Ar, J_1 = 5.7, J_2 = 11.3 Hz), 4.38 (dd, 1H, CHbH, J_1 = 17.8, J_2 = 11.3 Hz), 4.01 (s, 2H, CH_2), 3.59 (dd, 1H, CHHa, J_1 = 17.8, J_2 = 5.7 Hz), 3.22 (s, 3H, $COCH_3$).

3'-{4-(1-Acetyl-5-(4-methoxyphenyl)-2-pyrazoline-3-yl)phenyl}-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-diones 5c: IR (KBr, cm^{-1}): 3315 (N-H str.), 3074 (C-H str., Ar-H), 2981 (C-H str., CH_3), 1708, 1685 (C=O str.), 1624 (C=N str.), 1072 (C-O str.), 689 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ): 11.97 (s, 1H, isatin NH), 7.73-6.84 (m, 12H, Ar-H), 5.47 (dd, 1H, CH-Ar, J_1 = 5.7, J_2 = 11.3 Hz), 4.39 (dd, 1H, CHbH, J_1 = 17.8, J_2 = 11.3 Hz), 4.07 (s, 2H, CH_2), 3.90 (s, 3H, OCH_3), 3.61 (dd, 1H, CHHa, J_1 = 17.8, J_2 = 5.7 Hz), 3.16 (s, 3H, $COCH_3$).

3'-{4-(1-Acetyl-5-(4-nitrophenyl)-2-pyrazoline-3-yl)phenyl}-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-diones 5d: IR (KBr, cm^{-1}): 3312 (N-H str.), 3083 (C-H str., Ar-H), 2976 (C-H str., CH_3), 1705, 1688 (C=O str.), 1627 (C=N str.), 1540, 1346 (NO_2 asymm. and symm. str.), 682 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ): 11.94 (s, 1H, isatin NH), 7.70-6.89 (m, 12H, Ar-H), 5.47 (dd, 1H, CH-Ar, J_1 = 5.7, J_2 = 11.3 Hz), 4.40 (dd, 1H, CH*b*H, J_1 = 17.8, J_2 = 11.3 Hz), 4.14 (s, 2H, CH_2), 3.58 (dd, 1H, CHH*a*, J_1 = 17.8, J_2 = 5.7 Hz), 3.12 (s, 3H, $COCH_3$).

3'-{4-(1-Acetyl-5-phenyl-2-pyrazoline-3-yl)phenyl}-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-diones 5e: IR (KBr, cm^{-1}): 3305 (N-H str.), 3074 (C-H str., Ar-H), 2971 (C-H str., CH_3), 1709, 1682 (C=O str.), 1615 (C=N str.), 682 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ) : 11.98 (s, 1H, isatin NH), 7.68-6.89 (m, 13H, Ar-H), 5.50 (dd, 1H, CH-Ar, J_1 = 5.7, J_2 = 11.3 Hz), 4..37 (dd, 1H, CHbH, J_1 = 17.8, J_2 = 11.3 Hz), 3.98 (s, 2H, CH_2), 3.60 (dd, 1H, CHHa, J_1 = 17.8, J_2 = 5.7 Hz).

Synthesis of 3'-{4-(1-acetyl-5-(4-chlorophenyl)-2-pyrazoline-3-yl)phenyl}-1-*N*-ethoxyphthalimido-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-dione 6a: Compound **5a** (0.01 mole) was dissolved in 15 mL DMF and sodium hydride (0.01 mole) was added portion wise with constant stirring at 0-10 °C for 4 hr. Phthalimidoxy ethyl bromide (0.01 mole) was added to above mixture with constant stirring on a magnetic stirrer. Further the reaction-mixture was refluxed for 8-10 hr. Excess solvent was distilled off and the residual reaction-mixture was cooled and poured into ice-cold water. Solid obtained was recrystallized from ethanol.

IR (KBr, cm^{-1}): 3100 (C-H str., Ar-H), 2923 (C-H str., CH_3), 1713, 1687 (C=O str.), 1647 (C=N str.), 937 (N-O str.), 754 (C-Cl str.), 703 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ): 7.56-7.31 (m, 16H, Ar-H), 5.60 (dd, 1H, CH-Ar, J_1 = 5.4, J_2 = 11.6 Hz), 4.64 (t, 2H, OCH_2), 4.35 (dd, 1H, CHbH, J_1 = 17.5, J_2 = 11.6 Hz), 4.12 (s, 2H, S-CH_2), 3.50 (dd, 1H, CHHa, J_1 = 17.5, J_2 = 5.4 Hz), 3.12 (s, 3H, $COCH_3$), 2.93 (t, 2H, NCH_2); MS: *m/z* 705 $[M]^{+\cdot}$, 707 $[M+2]^{+\cdot}$, 677, 675, 663, 524, 221, 190, 162, 132.

Compounds **6b-e** were also synthesized by the similar method using appropriate reactants and minor modification in reaction conditions.

3'-{4-(1-Acetyl-5-(4-fluorophenyl)-2-pyrazoline-3-yl)phenyl}-1-*N*-ethoxyphthalimido-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-dione 6b: IR (KBr, cm^{-1}): 3110 (C-H str., Ar-H), 2913 (C-H str., CH_3), 1705, 1683 (C=O str.), 1642 (C=N str.), 1190 (C-F str.), 932 (N-O str.), 710 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ): 7.65-7.34 (m, 16H, Ar-H), 5.62 (dd, 1H, CH-Ar, J_1 = 5.4, J_2 = 11.6 Hz), 4.58 (t, 2H, OCH_2), 4.30 (dd, 1H, CHbH, J_1 = 17.5, J_2 = 11.6 Hz), 4.04 (s, 2H, S-CH_2), 3.48 (dd, 1H, CHHa, J_1 = 17.5, J_2 = 5.4 Hz), 3.08 (s, 3H, $COCH_3$), 2.89 (t, 2H, NCH_2); MS: *m/z* 689 $[M]^{+\cdot}$, 661, 659, 647, 645, 524, 205, 190, 165, 132, 104.

3'-{4-(1-Acetyl-5-(4-methoxyphenyl)-2-pyrazoline-3-yl)phenyl}-1-*N*-ethoxyphthalimido-4'*H*-spiro-[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-dione 6c: IR (KBr, cm^{-1}): 3106 (C-H str., Ar-H), 2917 (C-H str., CH_3), 1707, 1685 (C=O str.), 1638 (C=N str.), 1080 (C-O str.), 935 (N-O str.), 703 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ): 7.27-7.69 (m, 16H, Ar-H), 5.56 (dd, 1H, CH-Ar, J_1 = 5.4, J_2 = 11.6 Hz), 4.61 (t, 2H, OCH_2), 4.35 (dd, 1H, CHbH, J_1 = 17.5, J_2 = 11.6 Hz), 4.06 (s, 2H, S-CH_2), 3.48 (dd, 1H, CHHa, J_1 = 17.5, J_2 = 5.4 Hz), 3.18 (s, 3H, $COCH_3$), 2.90 (t, 2H, NCH_2); MS: *m/z* 701 $[M]^{+\cdot}$, 693, 671, 659, 524, 217, 162, 132, 104.

3'-{4-(1-Acetyl-5-(4-nitrophenyl)-2-pyrazoline-3-yl)phenyl}-1-*N*-ethoxyphthalimido-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-dione 6d: IR (KBr, cm^{-1}): 3116 (C-H str., Ar-H), 2932 (C-H str., CH_3), 1701, 1682 (C=O str.), 1624 (C=N str.), 1527, 1356 (NO_2 asymm. and symm. str.), 935 (N-O str.), 700 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ): 7.24-7.67 (m, 16H, Ar-H), 5.51 (dd, 1H, CH-Ar, J_1 = 5.4, J_2 = 11.6 Hz), 4.56 (t, 2H, OCH_2), 4.29 (dd, 1H, CHbH, J_1 = 17.5, J_2 = 11.6 Hz), 4.01 (s, 2H, S-CH_2), 3.43 (dd, 1H, CHHa, J_1 = 17.5, J_2 = 5.4 Hz), 3.11 (s, 3H, $COCH_3$), 2.91 (t, 2H, NCH_2); MS: *m/z* 716 $[M]^{+\cdot}$, 688, 686, 674, 524, 232, 192, 162, 132, 104.

3'-{4-(1-Acetyl-5-phenyl-2-pyrazoline-3-yl)phenyl}-1-*N*-ethoxyphthalimido-4'*H*-spiro[indole-3,2'-[1,3]thiazolidene]-2,4'-1*H*-dione 6e: IR (KBr, cm^{-1}): 3103 (C-H str., Ar-H), 2927 (C-H str., CH_3), 1704, 1684 (C=O str.), 1629 (C=N str.), 931 (N-O str.), 689 (C-S-C str.); ^{1}H NMR ($CDCl_3$, δ) : 7.21-7.64 (m, 16H, Ar-H), 5.53 (dd, 1H, CH-Ar, J_1 = 5.4, J_2 = 11.6 Hz), 4.62 (t, 2H, OCH_2), 4.33 (dd, 1H, CHbH, J_1 = 17.5, J_2 = 11.6 Hz), 4.01 (s, 2H, S-CH_2), 3.46 (dd, 1H, CHHa, J_1 = 17.5, J_2 = 5.4 Hz), 3.14 (s, 3H, $COCH_3$), 2.88 (t, 2H, NCH_2); MS: *m/z* 671 $[M]^{+\cdot}$, 643, 641, 629, 627, 524, 190, 187, 162, 147, 132, 104, 677, 675, 663, 524, 221, 190, 162, 132.

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