A facile synthesis of novel unsymmetrical bis-spiro[indole-pyrazolinyl-thiazolidine]-2,4'-diones

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Abstract
An elegant synthesis of some novel unsymmetrical bis-indol-2,3-diones (**4a-d**) has been achieved *via* 1-(6-bromohexyl)-1*H*-indol-2,3-diones (**3a,b**). These compounds have been further used for the synthesis of novel bis-spiroindoles (**7a-d**) via hitherto unknown bis Schiff's bases (**6a-d**).

Keywords: Schiff's bases, spiroindoles, unsymmetrical bis-heterocycles

Introduction

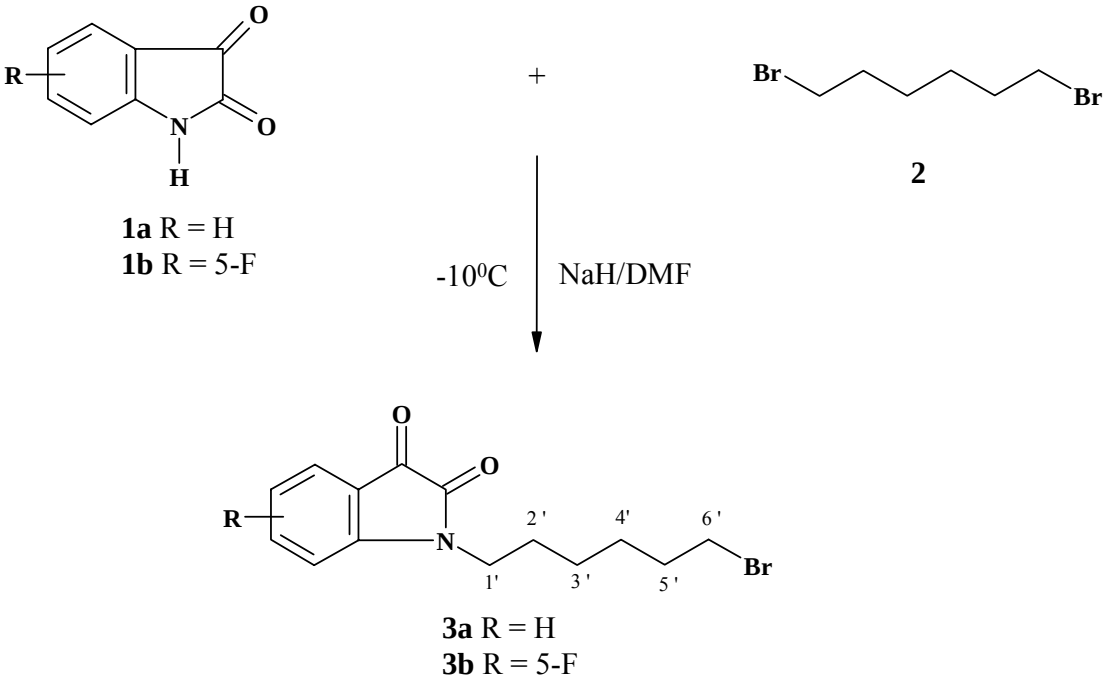
The discovery and development of heterocyclic systems of pharmaceutical importance has been of enormous interest to synthetic organic chemists owing to their presence in biological systems. Of the various heterocycles known, bis-heterocyclic compounds with a suitable alkyl spacer constitute an important class and have been under study for various types of activities, preferably, antitumor[1] and antimicrobial,[2] based on the DNA binding affinity and enzyme inhibiting actions. These activities, that result in their pharmacological utility, have been reported to be enhanced when different functionalities or substitutions are present on the two heterocyclic moieties in the bis-compound.[3,4] However, there have been very few reports of this type of unsymmetrical bis compounds containing indole as the basic heterocyclic moiety.

Thus, in continuation to our interest on spiro[5-7] and bis-spiro indoles,[8] we now wish to report the synthesis of some novel unsymmetrical bis-spiroindoles *via* their corresponding bis-Schiff's bases. These Schiff's bases were prepared from unsymmetrical bis-1*H*-indol-2,3-diones which in turn have been synthesised using 1-(6-bromohexyl)-1*H*-indol-2,3-diones as alkylating agents on differently substituted 1*H*-indol-2,3-diones in presence of sodium hydride as a base.

Results and Discussion

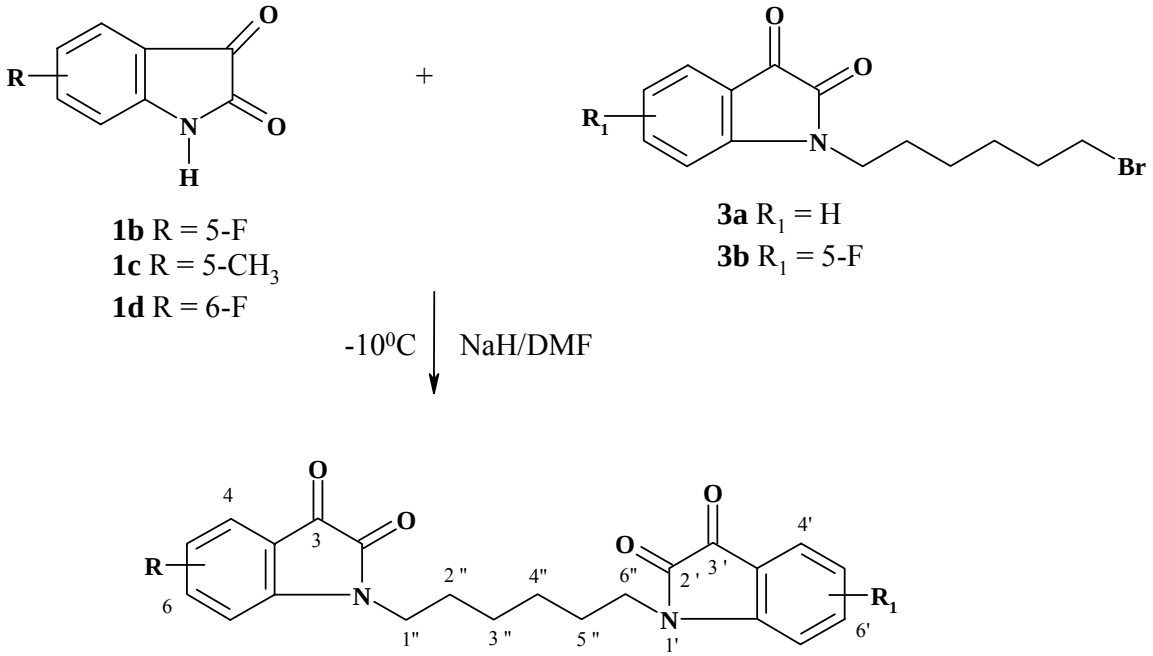
We have synthesised twelve novel bis-indolyl compounds in all besides two new 1-(6-bromohexyl)-1*H*-indol-2,3-diones.

The reaction of 1*H*-indol-2,3-dione (**1a**) with 1,6-dibromohexane (**2**) in 1:1 ratio in the presence of NaH/DMF at –10°C, has resulted in the formation of mono N-alkylated light orange solid **3a** as the major product along with its bis counterpart in minor amounts. Its IR spectrum showed characteristic carbonyl absorption bands at 1738 and 1735 cm^{-1}. Absence of absorption band in the region 3300-3400 cm^{-1} (>NH) indicated that N-alkylation has occurred in the indole moiety. This was supported by its ^{1}H NMR spectrum which displayed two triplets at δ 3.72 and δ 3.40, each integrating for two protons of $>NCH_2$ and $-CH_2$-Br respectively, indicating the presence of 6-bromohexyl group at the nitrogen of the indole moiety. The rest of the methylenes of the hexyl chain appeared as multiplets at δ 1.47, 1.70 and 1.90. The aromatic protons of the indole moiety appeared at δ 6.89 (H-7), δ 7.12 (H-5) and δ 7.56 (H-6 & H-4). In ^{13}C NMR spectrum, the series of methylenes appeared at δ 27.3, 27.7, 28.8, 29.0, 34.1 (**C**H_2-Br) and δ 41.7 (>N-**C**H_2). Also C-2 and C-3 carbonyl carbons showed signals at δ 175.2 and 185.1 respectively. In mass spectra, the molecular ion peak was observed at *m/z* 310. On the basis of these observations **3a** has been identified as 1-(6-bromohexyl)-1*H*-indol-2,3-dione(Scheme 1). **3a** and its 5-fluoro analogue have been used as alkylating agents on differently substituted isatins to obtain various unsymmetrical bis isatins.



Scheme 1

The reaction of 5-methyl-1*H*-indol-2,3-dione (**1c**) with 1-(6-bromohexyl)-1*H*-indol-2,3-dione (**3a**) in 1:1 ratio in the presence of NaH/DMF at –10°C resulted in the formation of a yellow solid **4a**. Its ^{1}H NMR spectra displayed a triplet at δ 3.71 integrating for four protons indicating thereby that two indole moieties have been linked together *via* nitrogen through an alkyl chain. The fact was further supported by the absence of –CH_2Br signal. The rest of the methylenes of the hexyl spacer appeared as multiplets at δ 1.43 and δ 1.69. A singlet at δ 2.32 integrating for three protons indicated a methyl group in an aromatic ring. The aromatic protons of the indole moieties appeared in the range δ 6.77 and δ 7.58, as expected. Formation of bis product has finally been confirmed on the basis of its mass spectra which showed a molecular ion peak at *m/z* 390, corresponding to its molecular formula. On the basis of these spectral data **4a** has been identified as 5-methyl-1-[6-(2,3-dioxoindolyl)hexyl]-1*H*-indol-2,3-dione(Scheme 2).



4a R = 5-CH_3, R_1 = H
4b R = 5-CH_3, R_1 = 5-F
4c R = 6-F, R_1 = 5-F
4d R = 5-F, R_1 = H

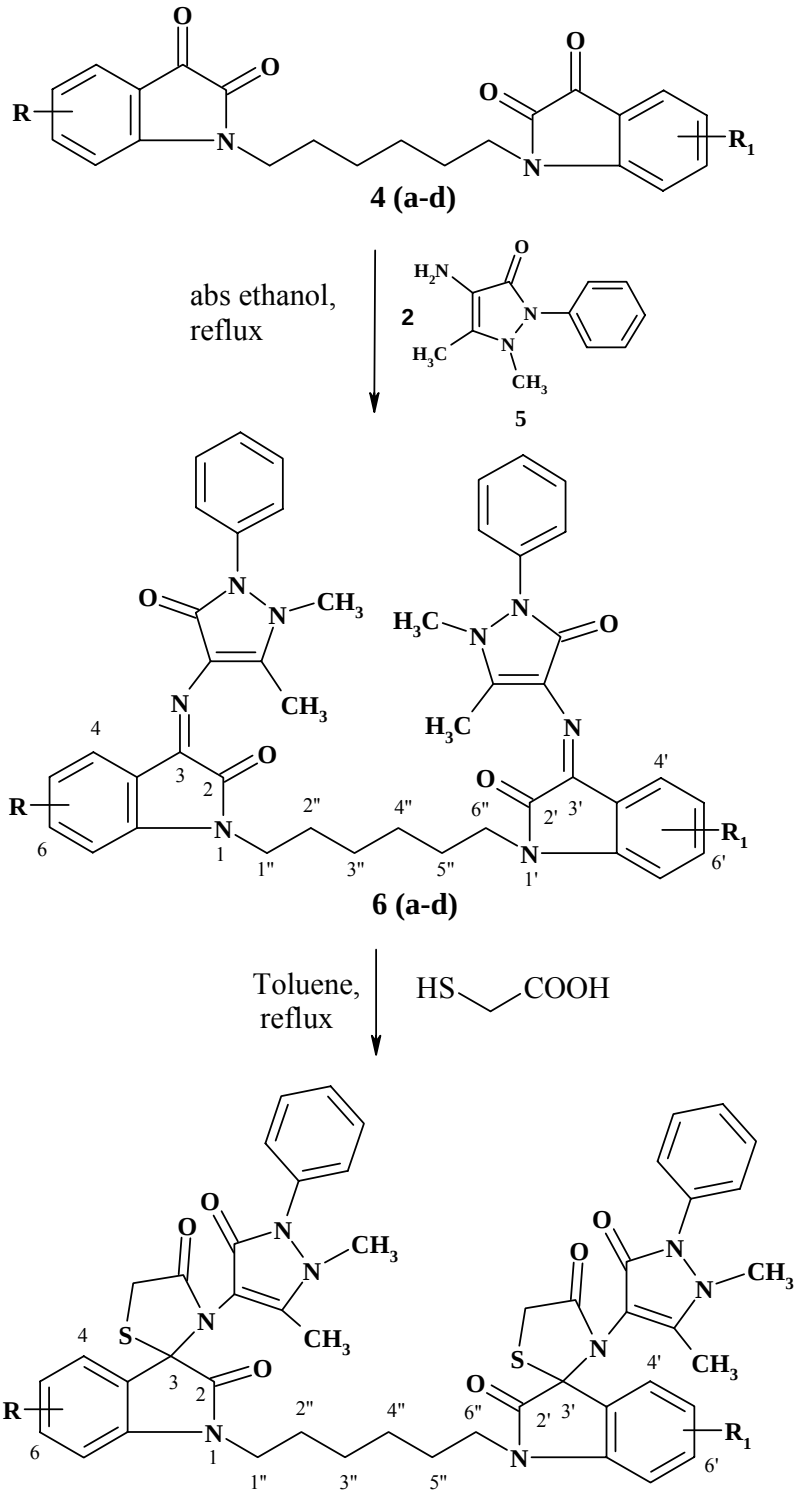
Scheme 2

The reaction of **4a** with 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**5**) in 1:2 ratio, in absolute ethanol, yielded a Schiff's base as an orange coloured solid. Its molecular ion peak, at m/z 760 in FAB-MS, corresponded to the molecular formula $C_{45}H_{44}O_4N_8$ for the expected Schiff's base. This got further support from its IR spectrum which showed a characteristic >C=N- absorption band at 1650 cm^{-1}. Its ^{1}H NMR spectrum displayed singlets at δ 3.24 & δ 2.43

each integrating for six protons showing the presence of two pairs of methyl groups of the pyrazoline moieties. However, the peak for the methyl substituent of indole integrating for three protons appeared at δ 2.30. Further, multiplets at δ 7.43 and 6.70 integrating for ten and seven protons, indicated the presence of two phenyl groups of the pyrazoline moieties and aromatic protons of the indole nuclei, respectively. The triplet appearing at δ 3.71 integrating for four protons showed the presence of two >N-CH_2 moieties linked by methylenes spacer that appeared as multiplet at δ 1.42 (4H, 2xCH_2) and 1.68 (4H, 2xCH_2). ^{13}C NMR spectrum displayed characteristic carbonyl signals at δ 166.2 (lactam) and δ 165.2 (pyrazoline), in addition to a signal at δ 151.1 confirming the presence of (>C=N-) at C-3 and C-3' in the molecule. The above spectral studies confirmed the formation of an unsymmetrical Schiff's base which was characterized as 5-methyl-1-[6-(3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)imino-2-oxo-indolyl)hexyl]-3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) imino-1*H*-indol-2-one **(6a)** (Scheme 3).

The cyclocondensation reaction of **6a** was carried out with mercaptoacetic acid under refluxing conditions using Dean-Stark apparatus to yield a white solid **7a**. Its FAB-MS showed the molecular ion peak at m/z 908, corresponding to the molecular formula $C_{49}H_{48}O_6N_8S_2$,. The IR spectrum showed the presence of characteristic absorptions at 1715(thiazolidinone carbonyl), 1690(lactam carbonyl) and 1678 (pyrazolinyl carbonyl) cm^{-1} indicating that cycloaddition has occurred. However, the confirmation came from ^{1}H NMR spectrum as two doublets appeared at δ 4.32 & 4.48 which integrated for four protons of the two methylenes of the thiazolidinone rings in the molecule. The remaining protons of the alkyl spacer, indole and pyrazoline moieties appeared at usual chemical shifts. ^{13}C NMR spectra showed characteristic peaks at δ 174.2 (thiazolidine carbonyl), δ 171.2 (lactam carbonyl), δ 162.2 (pyrazoline carbonyl), δ 110.4-145.1 (aromatic carbons) along with methyl carbons at δ 35.1 (-NCH_3) and δ 13.3 (pyrazolin-CH_3) of pyrazoline moiety and methylene carbons at δ 41.5, 29.2 and 28.5. The characteristic methylene (S-CH_2) of thiazolidine moieties appeared at δ 32.2. The N-CH_3 and S-CH_2 carbons have been distinguished on the basis of DEPT-135 experiment.

On the basis of above spectral studies **7a** was assigned structure as 5-methyl-1-[6-(3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)spiro(3*H*-indol-3,2'-thiazolidine)-2,4'-dione-1-yl)hexyl]-3'-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)spiro(3*H*-indol-3,2′-thiazolidine)-2,4'-dione(Scheme 3).



7a R = 5-CH_3, R_1 = H
7b R = 5-CH_3, R_1 = 5-F
7c R = 6-F, R_1 = 5-F
7d R = 5-F, R_1 = H

Scheme 3

Experimental Section

General Procedures. Melting points were determined in a capillary tube in sulphuric acid bath and are uncorrected. IR spectra were recorded on Shimadzu model IR-435 spectrophotometer. ^{1}H NMR spectra were recorded on Bruker AC (300 MHz) in $CDCl_3$. ^{13}C NMR spectra were recorded on Bruker AC (75.47 MHz) in $CDCl_3$. Elemental analyses were performed on a Perkin Elmer series 11, CHNS/O analyzer 2400.Mass spectra were recorded on Jeol-JMS-DX 303 mass spectrometer. Substituted indol-2,3-diones were prepared by literature procedures starting from the corresponding anilines.[5-8]

1-(6-Bromohexyl)-1*H*-indol-2,3-dione (3a). 1*H*-Indol-2,3-dione (**1a**) (1 g, 6.80 mmol) in 10 ml of DMF was added dropwise during 20 minutes at -10°C to a well stirred solution of sodium hydride under inert atmosphere of nitrogen. To the deep purple coloured suspension that resulted, 1,6-dibromohexane (**2**) (1.65 g, 6.80 mmol) was added dropwise during 20 min at -10°C. The contents were allowed to stir over night at room temperature and then quenched with ice water to obtain a red coloured semi solid. This was extracted with chloroform and purified by column chromatography using silica gel as an adsorbent to obtain **3a**. Yield 82%, m.p. 72°C; IR(KBr)cm^{-1}: 1738, 1735, 1611, 1470, 1355, 1301, 1270, 1189, 1162, 1051, 955, 754; ^{1}H NMR (δ, $CDCl_3$): 1.47 (m, 4H, H-3′ & H-4′), 1.70 & 1.90 (2m, 4H, H-2′ & H-5′), 3.40 (t, 2H, *J* = 6.6 Hz, H-6′), 3.72 (t, 2H, *J* = 7.5 Hz, H-1′), 6.89 (d, 1H, *J* = 8.1 Hz, H-7), 7.12 (d, 1H, *J* = 7.5 Hz, H-5), 7.56 (m, 2H, H-4 & H-6); ^{13}C NMR (δ, $CDCl_3$): 27.3, 27.7, 28.8, 29.0 (C-2′, C-3′, C-4′ & C-5′), 34.1 (C-6′), 41.7 (C-1′), 111.7, 119.3, 127.1, 140.0, 152.6, 159.8, 175.2 (C-2), 185.1 (C-3); EIMS, m/z: 312 (M^++2), 310 (M^+), 230 (M^+-Br), 210, 202, 174, 160, 146, 132, 118, 104, 90, 77. Anal. Calcd for $C_{14}H_{16}NO_2Br$: C, 54.19; H, 5.16; N, 4.51. Found: C, 54.26; H, 5.11; N, 4.57.

Compound **3b** was synthesized using the above mentioned procedure.
1-(6-Bromohexyl)-5-fluoro-1*H*-indol-2,3-dione (3b). Yield 85%, m.p.76°C; IR(KBr) cm^{-1}: 1739, 1733, 1622, 1608, 1485, 1343, 1266, 1223, 1126, 1104, 886, 824, 781; ^{1}H NMR (δ, $CDCl_3$): 1.51 (m, 4H, H-3′ & H-4′), 1.73 & 1.85 (2m, 4H, H-2′ & H-5′), 3.40 (t, 2H, *J* = 6.6.Hz, H-6′), 3.73 (t, 2H, *J* = 7.2 Hz, H-1′), 6.86 (m, 1H, H-7), 7.29 (m, 2H, H-4 & H-6); ^{13}C NMR (δ, $CDCl_3$): 27.5, 27.8, 28.8, 29.4(C-2′, C-3′, C-4′ & C-5′), 34.2 (C-6′), 42.0 (C-1′), 112.9 114.2, 126.2, 136.12, 155.0, 158.1, 174.2 (C-2), 184.2 (C-3); EIMS, m/z: 330 (M^++2), 328 (M^+), 300, 248 (M^+-Br), 221, 193, 179, 165, 164, 150, 137, 122, 108, 95, 75. Anal. Calcd for $C_{14}H_{15}NO_2BrF$: C, 51.21; H, 4.57; N, 4.26. Found: C, 51.28; H, 4.61; N, 4.20.

5-Methyl-1-[6-(2,3-dioxoindolyl)hexyl]-1*H*-indol-2,3-dione (4a). To a stirred solution of NaH in 50 ml of dry DMF, a solution of 5-methyl-1*H*-indol-2,3-dione (**1c**) (1g, 3.2mmol) in DMF (5 ml) was added dropwise during 20 min. at –10°C under inert atmosphere of nitrogen. To a resulting deep purple coloured suspension, 1-(6-bromohexyl)-1*H*-indol-2,3-dione (**3a**) (510 mg, 3.2 mmol) in DMF was added dropwise during 20 min. at –10°C. The contents were allowed to

stir overnight at room temperature. The reaction mixture was then quenched with ice water and a red coloured solid obtained was filtered and purified by column chromatography to obtain **4a.** Yield 75%, m.p.192°C; IR(KBr) cm^{-1}: 1733, 1613, 1489, 1466, 1348, 1287, 1158, 1125, 1094, 754, 473; ^{1}H NMR (δ, $CDCl_3$): 1.43 (m, 4H, H-3″ & H-4″), 1.69 (m, 4H, H-2″ & H-5″), 2.32 (s, 3H, 5-CH_3), 3.71 (t, 4H, *J* = 6.9 Hz, H-1″ & H-6″), 6.77 & 6.87 (2d, 1H each, *J* = 7.5 & 8.1 Hz, H-7 & H-7′), 7.11 (t, 1H, *J* = 7.5 Hz, H-5′), 7.38 (m, 2H, H-4 & H-4′), 7.58 (m, 2H, H-6 & H-6′); ^{13}C NMR (δ, $CDCl_3$): 20.7 (5-CH_3), 27.8 (C-3″ & C-4″), 28.8 (C-2″ & C-5″), 41.7 (C-1″ & C-6″), 111.7, 119.3, 125.3, 127.1, 134.1, 140.0, 152.8, 159.8, 174.3 (C-2 & C-2′), 185.1 (C-3 & C-3′); EIMS, m/z: 390 (M^+), 327, 248, 216, 202, 188, 174, 160, 146, 132, 118, 105, 91, 83, 77. Anal. Calcd for $C_{23}H_{22}N_2O_4$: C, 70.76; H, 5.64; N, 7.17. Found: C, 70.71; H, 5.68; N, 7.26.

Compounds **4b-d** were synthesized using the similar procedure as described for **4a**.

5-Fluoro-1-[6-(5-methyl-2,3-dioxoindolyl)hexyl]-1*H*-indol-2,3-dione (4b). Yield 72%, m.p.198°C; IR(KBr)cm^{-1}: 1732, 1619, 1486, 1341, 1268, 1157, 1124, 842, 710, 472; ^{1}H NMR (δ, $CDCl_3$): 1.42 (m, 4H, H-3″ & H-4″), 1.69 (m, 4H, H-2″ & H-5″), 2.33 (3H, 5-CH_3), 3.71 (t, 4H, J = 6.9 Hz, H-1″ & H-6″), 6.81 (m, 2H, H-7 & H-7′), 7.35 (m, 4H, H-4, H-6, H-4′ & H-6′); ^{13}C NMR (δ, $CDCl_3$): 20.9 (5-CH_3), 26.5 (C-3″ & C-4″),27.3 (C-2″ & C-5″), 40.3 (C-1″ & C-6″), 110.2, 111.5, 117.2, 118.0, 124.8, 126.2, 133.3, 139.0, 149.0, 158.7, 178.3 (C-2 & C-2′), 190.2 (C-3 & C-3′); EIMS, m/z: 408 (M^+), 390, 345, 214, 200, 186, 175, 164, 161, 146, 132, 119, 104, 91, 77, 65, 55, 41. Anal. Calcd for $C_{23}H_{21}N_2O_4F$: C, 67.64; H, 5.14; N, 6.86. Found: C, 67.70; H, 5.19; N, 6.81.

5-Fluoro-1-[6-(6-fluoro-2,3-dioxoindolyl)hexyl]-1*H*-indol-2,3-dione (4c). Yield 82%, m.p. 202°C; IR(KBr)cm^{-1}: 1700, 1657, 1610, 1465, 1377, 1158, 757**;** ^{1}H NMR (δ, $CDCl_3$): 1.37 (m, 4H, H-3″ & H-4″), 1.70 (m, 4H, H-2″ & H-5″), 3.68 (t, 4H, *J* = 7.2 Hz, H-1″ & H-6″) 6.78 (d, 2H, *J* = 7.8 Hz, H-7 & H-7′), 7.38 (m, 4H, H-4, H-5, H-4′ & H-6′); ^{13}C NMR (δ, $CDCl_3$): 27.2 (C-3″ & C-4″), 29.3 (C-2″ & C-5″), 40.7 (C-1″ & C-6″), 111.50, 111.6, 112.7, 113.0, 120.5, 124.7, 125.0, 133.5, 158.1, 160.2, 173.2 (C-2 & C-2′), 185.2 (C-3 & C-3′); EIMS, m/z: 412 (M^+), 288, 230, 202, 188, 164, 150, 136, 122, 108, 77. Anal. Calcd for $C_{22}H_{18}N_2O_4F_2$: C, 64.07; H, 4.36; N, 6.79. Found: C, 64.13; H, 4.32; N, 6.72.

5-Fluoro-1-[6-(2,3-dioxoindolyl)hexyl]-1*H*-indol-2,3-dione (4d). Yield 78%, m.p. 192°C; IR(KBr) cm^{-1}: 1736, 1611, 1485, 1356, 1268, 1162, 1094, 885, 755, 609, 474; ^{1}H NMR (δ, $CDCl_3$): 1.43 (m, 4H, H-3″ & H-4″), 1.70 (m, 4H, H-2″ & H-5″), 3.71 (t, 4H, *J* = 7.2 Hz, H-1″ & H-6″), 6.88 (m, 2H, H-7 & H-7′), 7.16 & 7.38 (2m, 5H, H-4, H-6, H-4′, H-5′ & H-6′); ^{13}C NMR (δ, $CDCl_3$): 26.7 (C-3″ & C-4″), 27.4 (C-2″ & C-5″), 40.3 (C-1″ & C-6″), 110.5, 111.7, 113.0, 124.0, 124.9, 125.4, 125.8,138.7, 147.3, 151.2, 161.2 (C-2 & C-2′), 185.2 (C-3 & C-3′); EIMS, m/z: 394 (M^+), 178, 174, 164, 160, 146, 132, 118. Anal. Calcd for $C_{22}H_{19}N_2O_4F$: C, 67.00; H, 4.82; N, 7.10. Found: C, 67.06; H, 4.75; N, 7.03.

5-Methyl-1-[6-(3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)imino-2-oxo-indolyl)hexyl]-3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) imino-1*H*-indol-2-one (6a). A mixture 5-

methyl-1-[6-(2,3-dioxoindolyl)hexyl]-1*H*-indol-2,3-dione (**4a**) (780mg, 2mmol) and 4-amino-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**5**) (812mg, 4mmol) in absolute ethanol (20ml) was refluxed at 80°C for 8 hours. The compound that separated out on cooling, was filtered, washed with ethanol and crystallized from chloroform/methanol as orange solid **6a**.Yield 82%, m.p. 198°C; IR(KBr)cm^{-1}: 1714, 1650, 1593, 1542, 1490, 1357, 1171, 1026, 744, 697, 550, 506; ^{1}H NMR (δ, $CDCl_3$):1.42 (m, 4H, H-3′′ & H-4′′), 1.68 (m, 4H, H-2′′ & H-5′′), 2.30 (s, 3H, 5-CH_3), 2.43 (s, 6H, 2xCH_3), 3.24 (s, 6H, 2x N-CH_3), 3.71 (t, 4H, *J* = 6.5 Hz, H-1′′ & H-6′′), 6.70 (m, 7H, H-4, H-6, H-7, H-4′, H-5′, H-6′ & H-7′), 7.43 (m, 10H, 2xN-C_6H_5); ^{13}C NMR (δ, $CDCl_3$): 13.3 (pyrazoline-CH_3), 23.1 (5-CH_3), 28.5 (C-3′′ & C-4′′), 29.3 (C-2′′ & C-5′′), 38.1 (N-CH_3), 41.8 (C-1′′& C-6′′), 110.3-134.9 (aromatic carbons), 151.1 (C-3 & C-3′), 165.2 (pyrazoline >C=O), 166.2 (C-2 & C-2′); MS(FAB), m/z: 760. Anal. Calcd for $C_{45}H_{44}N_8O_4$: C, 71.05; H, 5.78; N, 14.73. Found: C, 71.12; H, 5.73; N, 14.82.

Compounds **6b-d** were synthesized using similar procedure as above.

5-Fluoro-1-[6-(5-methyl-3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)imino-2-oxo-indolyl)hexyl]-3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) imino-1*H*-indol-2-one (6b). Yield 76%, m.p. 210°C, IR(KBr)cm^{-1}: 1716, 1645, 1589, 1488, 1456, 1348, 1308, 1160, 1126, 1034, 856, 815, 765, 696, 620, 574, 501; ^{1}H NMR (δ, $CDCl_3$): 1.40 (m, 4H, H-3′′ & H-4′′), 1.63 (m, 4H, H-2′′ & H-5′′), 2.32 (s, 3H, 5-CH_3), 2.43 (6H, 2xCH_3), 3.23 (s, 6H, 2xN-CH_3), 3.73 (t, 4H, *J* = 6.0 Hz, H-1′′ & H-6′′), 6.70 (m, 2H, H-7 & H-7′). 7.35 (m, 14H, H-4, H-6, H-4′,H-6′ & 2xN- C_6H_5); ^{13}C NMR (δ, $CDCl_3$): 13.3 (pyrazoline-CH_3), 22.8 (5-CH_3), 28.5 (C-3′′ & C-4′′), 29.2 (C-2′′ & C-5′′), 38.0 (N-CH_3), 41.9 (C-1′′& C-6′′), 110.4-136.1 (aromatic carbons), 153.2 (C-3 & C-3′), 162.2 (pyrazoline >C=O), 168.1 (C-2 & C-2′); MS(FAB), m/z: 778. Anal. Calcd for $C_{45}H_{43}N_8O_4F$: C, 69.40; H, 5.52; N, 14.39. Found: C, 69.48; H, 5.59; N, 14.30.

5-Fluoro-1-[6-(6-fluoro-3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)imino-2-oxo-indolyl)hexyl]-3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) imino-1*H*-indol-2-one (6c). Yield 82%, m.p. 212°C; IR(KBr)cm^{-1}: 1720, 1643, 1592, 1542, 1486, 1413, 1346, 1274, 1182, 1106, 857, 760, 698, 548; ^{1}H NMR (δ, $CDCl_3$): 1.36 (m, 4H, H-3′′ & H-4′′), 1.70 (m, 4H, H-2′′ & H-5′′), 2.45 (s, 6H, 2xCH_3), 3.25 (s, 6H, 2x N-CH_3), 3.73 (t, 4H, J = 6.8 Hz, H-1′′ & H-6′′), 6.82 (m, 2H, H-7 & H-7′), 7.06 (m, 4H, H-4, H-5, H-4′ & H-6′), 7.44 (m, 10H, 2xN- C_6H_5); ^{13}C NMR (δ, $CDCl_3$): 11.2 (pyrazoline-CH_3), 26.4 (C-3′′ & C-4′′), 30.4 (C-2′′ & C-5′′), 32.4 (N-CH_3), 39.8 (C-1′′ & C-6′′), 108.2-140.4 (aromatic carbons), 151.0 (C-3 & C-3′), 165.2 (pyrazoline >C=O), 166.8 (C-2 & C-2′); MS(FAB), m/z: 782. Anal. Calcd for $C_{44}H_{40}N_8O_4F_2$: C, 67.51; H, 5.11; N, 14.32. Found: C, 67.55; H, 5.18; N, 14.24.

5-Fluoro-1-[6-(3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)imino-2-oxo-indolyl)hexyl]-3-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) imino-1*H*-indol-2-one (6d). Yield 82%, m.p. 203°C; IR(KBr)cm^{-1}: 1716, 1646, 1592, 1485, 1350, 1158, 1101, 817, 764, 695, 574, 501; ^{1}H NMR (δ, $CDCl_3$): 1.45 (m, 4H, H-3′′ & H-4′′), 1.68 (m, 4H, H-2′′ & H-5′′), 2.47 (s, 6H, 2xCH_3), 3.29 (s, 6H, 2xN-CH_3), 3.74 (t, 4H, J = 6.6 Hz, H-1′′ & H-6′′), 6.74 (m, 2H, H-7 & H-7′), 6.80 & 7.20 (2m, 15H, H-4, H-6, H-4′, H-5′, H-6′ & 2xN-C_6H_5); ^{13}C NMR (δ, $CDCl_3$): 13.3

(pyrazoline-CH_3), 28.5 (C-3″ & C-4″), 29.2 (C-2″ & C-5″), 38.0 (N-CH_3), 41.9 (C-1″& C-6″), 110.4 –136.1 (aromatic carbons), 153.2 (C-3 & C-3′), 162.2 (pyrazoline >C=O), 168.2 (C-2 & C-2′); MS(FAB), m/z: 764. Anal. Calcd for $C_{44}H_{41}N_8O_4F$: C, 69.10; H, 5.36; N, 14.65. Found: C, 69.16; H, 5.43; N, 14.73.

5-Methyl-1-[6-(3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)spiro(3*H*-indol-3,2′-thiazolidine)-2,4′-dione-1-yl)hexyl]-3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) spiro(3*H*-indol-3,2′-thiazolidine)-2,4′-dione (7a). A mixture of **6a** (152 mg, 0.2mmol) and mercaptoacetic acid (46 mg, 0.5 mmol) was taken in dry toluene in a round-bottom flask fitted with Dean-Stark apparatus. The contents were refluxed for about 8-9 hours with simultaneous removal of water azeotropically. The solution turned light yellow and sticky yellow compound thus formed was found to be different from the starting material. Toluene was removed on rotatory evaporator and the residue left was treated with saturated solution of sodium bicarbonate to remove excess acid. The solid left was filtered, washed with water, dried and crystallized from chloroform/methanol as creamy solid **7a**. Yield 80%, m.p. 97°C; IR(KBr)cm^{-1}: 3430, 2920, 1715, 1690, 1678, 1615, 1510, 1470, 1463, 1289, 1159, 1080, 763; ^{1}H NMR (δ, $CDCl_3$): 1.39, (m, 4H, H-3″ & H-4″), 1.65 (m, 4H, H-2″ & H-5″), 2.11 (s, 6H, pyrazoline-CH_3), 2.34 (s, 3H, 5-CH_3), 2.97 (s, 6H, 2xN-CH_3), 3.65 (m, 4H, H-1″ & H-6″), 4.32 & 4.48 (2d, 4H, *J*=14.8, each 2xS-CH_2), 6.69 (d, 2H, *J* = 6.0 Hz, H-7 & H-7′), 7.02 (m, 5H, H-4, H-6, H-4′, H-5′ & H-6′), 7.29 (m, 10H, 2xN- C_6H_5); ^{13}C NMR (δ, $CDCl_3$):13.3 (pyrazoline-CH_3), 20.3 (5-CH_3), 28.5 (C-3″ &C-4″), 29.2 (C-2″ & C-5″), 32.2 (S-CH_2), 35.1 (N-CH_3), 41.5 (C-1″ & C-6″), 110.4-145.1 (aromatic carbons), 162.2 (pyrazoline >C=O), 171.2 (C-2 & C-2′), 174.2 (thiazolidine >C=O); MS(FAB), m/z: 908. Anal. Calcd for $C_{49}H_{48}N_8O_6S_2$: C, 64.75; H, 5.28; N, 12.33. Found: C, 64.81; H, 5.17; N, 12.42.

Compounds **7b-d** were synthesized using similar procedure as above.

5-Fluoro-1-[6-(3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)spiro(5-methyl-3*H*-indol-3,2′-thiazolidine)-2,4′-dione-1-yl)hexyl]-3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) spiro(3*H*-indol-3,2′-thiazolidine)-2,4′-dione (7b). Yield 62%, m.p. 105°C; IR(KBr)cm^{-1}: 3435, 2925, 1719, 1674, 1611, 1488, 1467, 1355, 1289, 1160, 1130, 1090, 750; ^{1}H NMR (δ, $CDCl_3$): 1.36 (m, 4H, H-3″ & H-4″), 1.62 (m, 4H, H-2″ & H-5″), 2.21(s, 6H, 2xCH_3), 2.33 (s, 3H, 5-CH_3), 3.01 (s, 6H,2xN-CH_3), 3.64 (m, 4H, H-1″ & H-6″), 3.68 & 4.28 (2d, 4H, *J* = 15.0 Hz, each 2xS-CH_2), 6.59 (d, 2H, *J* = 7.2 Hz, H-7 & H-7′), 7.21 (14H, H-4, H-6, H-4′, H-6′ & 2xN- C_6H_5); ^{13}C NMR (δ, $CDCl_3$): 12.5 (pyrazoline-CH_3), 22.9 (5-CH_3), 28.2 (C-3″ &C-4″), 28.9 (C-2″ & C-5″), 34.7 (S-CH_2), 35.1 (N-CH_3), 42.2 (C-1″ & C-6″), 110.1-149.5 (aromatic carbons), 161.1 (pyrazoline >C=O), 168.1 (C-2 & C-2′), 170.1 (thiazolidine >C=O); MS(FAB), m/z: 926. Anal. Calcd for $C_{49}H_{47}N_8O_6S_2F$: C, 63.49; H, 5.07; N, 12.09. Found: C, 63.55; H, 5.01; N, 12.17.

5-Fluoro-1-[6-(3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)spiro(6-fluoro-3*H*-indol-3,2′-thiazolidine)-2,4′-dione-1-yl)hexyl]-3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) spiro(3*H*-indol-3,2′-thiazolidine)-2,4′-dione (7c). Yield 55%, m.p. 107°C; IR(KBr)cm^{-1}: 1718, 1685, 1649, 1572, 1467, 1392, 1315, 1199, 1024, 909, 852, 752; ^{1}H NMR (δ, $CDCl_3$): 1.26 (m,

4H, H-3″ & H-4″), 1.59 (m, 4H, H-2″ & H-5″), 2.07 (s, 6H, 2xCH_3), 2.93 (s, 6H, 2xN-CH_3), 3.64 (m, 4H, H-1″ & H-6″), 3.78 & 4.49 (2d, 4H, *J* = 14.7 Hz, each 2xS-CH_2), 6.69 (d, 2H, *J* = 7.0 Hz, H-7 & H-7′), 7.07, 7.20 & 7.29 (3m, 14H, H-4, H-5, H-4′, H-6′ & 2xN- C_6H_5); ^{13}C NMR (δ, $CDCl_3$): 14.2 (pyrazoline-CH_3), 25.6 (C-3″ &C-4″), 30.2 (C-2″ & C-5″), 35.8 (S-CH_2), 38.1 (N-CH_3), 43.6 (C-1″ & C-6″), 110.5-134.3 (aromatic carbons), 158.9 (pyrazoline >C=O), 164.3 (C-2 & C-2′), 174.1 (thiazolidine >C=O); MS(FAB), m/z: 930. Anal. Calcd for $C_{48}H_{44}N_8O_6S_2F_2$: C, 61.93; H, 4.73; N, 12.04. Found: C, 61.86; H, 4.80; N, 12.12.

5-Fluoro-1-[6-(3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl)spiro(3*H*-indol-3,2′-thiazolidine)-2,4′-dione-1-yl)hexyl]-3′-(2,3-dimethyl-5-oxo-1-phenyl-3-pyrazolin-4-yl) spiro(3*H*-indol-3,2′-thiazolidine)-2,4′-dione (7d). Yield 56%, m.p. 98°C; IR(KBr)cm^{-1}: 1720, 1695, 1682, 1613, 1490, 1460, 1351, 1158, 825, 752, 696, 593; ^{1}H NMR (δ, $CDCl_3$): 1.38, (m, 4H, H-3″ & H-4″), 1.64 (m, 4H, H-2″ & H-5″), 2.22 (s, 6H, 2xCH_3), 3.02 (s, 6H, 2x N-CH_3), 3.64 (t, 4H, *J* = 7.0 Hz, H-1″ & H-6″), 3.81 & 4.79 (2d, 4H, *J* = 14.5 Hz each, 2xS-CH_2), 6.71 (m, 2H, H-7 & H-7′), 7.23 & 7.50 (2m, 15H, H-4, H-6, H-4′, H-5′, H-6′ & 2xN-C_6H_5); ^{13}C NMR (δ, $CDCl_3$): 13.9 (pyrazoline-CH_3), 27.3 (C-3″ & C-4″), 30.0 (C-2″ & C-5″), 35.7 (S-CH_2), 36.1 (N-CH_3), 42.2 (C-1″ & C-6″), 111.4-143.1 (aromatic carbons), 164.1(pyrazoline >C=O), 170.2 (C-2 & C-2′), 173.2 (thiazolidine >C=O); MS(FAB), m/z: 912. Anal. Calcd for $C_{48}H_{45}N_8O_6S_2F$: C, 63.15; H, 4.93; N, 12.28. Found: C, 63.25; H, 5.01; N, 12.19.

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