One-pot rapid and efficient synthesis of new spiro derivatives of 11*H*-indeno[1,2-*b*]quinoxalin-11-one, 6*H*-indeno[1,2-*b*]pyrido [3,2-*e*]pyrazin-6-one and isatin-based 2-pyrazolines

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Abstract

Some new spiro derivatives (**5a-h**, **9a-c** and **13a-c**) of 11*H*-indeno[1,2-*b*]quinoxalin-11-ones **1a-b** and 6*H*-indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6-one **6** and isatin **10** were synthesized by two different pathways. The chalcones **4a-h**, **8a-c** and **12a-c** were prepared by the reaction of acetophenone and its four derivatives with **1a-b**, **6** and **10** via base-catalyzed condensation followed by addition of acid. In the first procedure, the chalcones were isolated and reacted with hydrazine hydrate to give products. In the second procedure, the chalcones were *in situ* reacted with hydrazine hydrate without isolation to give spiro compounds in improved yields.

Keywords: Spiro compounds, indenoquinoxalines, indenopyridopyrazines, isatin, pyrazolines

Introduction

Nitrogen containing heterocycles are frequently found in privileged structures (pharmacophores) [1-3] but their incorporation sometimes possess special problems (multistep sequences, lack of generality, preparation from acyclic precursors, etc.); thus, only a limited number of strategies have been successfully applied in the synthesis of heterocyclic scaffolds.[4-10] The development of new, rapid, and clean synthetic routes toward focused libraries of such compounds is therefore of great importance to both medicinal and synthetic chemists.[11-14] Consequently, the design

and development of procedures for the generation of new heterocycles receives growing interest.[15-17]

Indenoquinoxaline derivatives are important classes of nitrogen containing heterocycles and they constitute useful intermediates in organic synthesis.[18-20] They have been reported for their applications in dyes and have also been used as building blocks for the synthesis of organic semiconductors. More interestingly studies have discovered that these compounds exhibit diverse medical functions such as antimetabolism and antitubercular properties. [21, 22]

Isatin is an endogenous compound identified in humans that possesses wide range of biological activities. Isatin has anxiogenic, [23] anticonvulsant [24] activity and acts as a potent antagonist on atrial natriuretic peptide receptors *in vitro*.[25] Isatin derivatives of Mannich bases had antibacterial, [26-28] antifungal, [29-31] antiviral, [32-34] anti HIV, [35-37] antiprotozoal, [38, 39] anticancer, [40] muscle relaxant, [41] antiallergic [42] activity.

Pyrazolines can be effectively utilized as antibacterial, antifungal, antiviral, antiparasitic, antitubercular, antidepressant and insecticidal agents and considerable attention has been focused on this class.[43-49] In addition, pyrazolines have played a crucial part in the development of theory in heterocyclic chemistry and also used extensively in organic synthesis. [50, 51]After the pioneering work of Fischer and Knövenagel in the late nineteenth century,[52] the reaction of α,β-unsaturated aldehydes and ketones with hydrazines became one of the most popular methods for the preparation of 2-pyrazolines. [53-61]

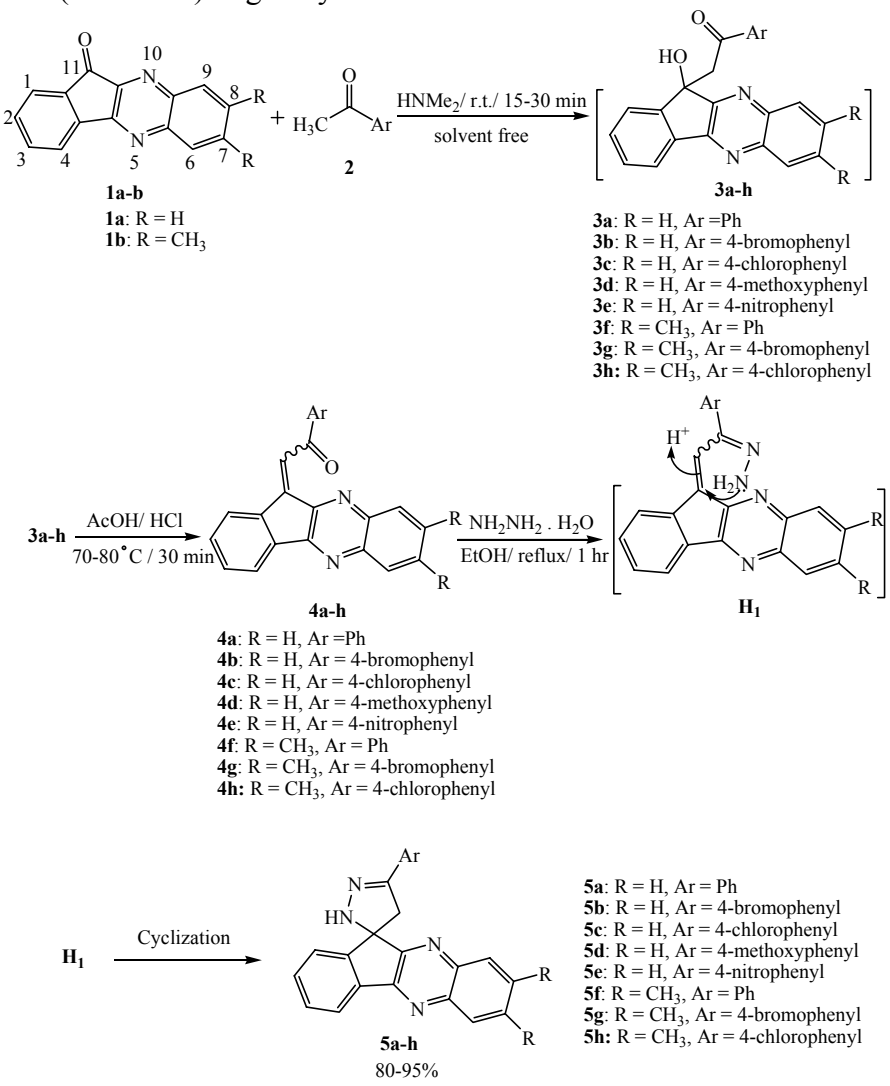
Giving attention to the possible biological effects of the presence of both 2-pyrazoline and indenoquinoxaline or isatin moieties in an organic compound, it appeared useful to synthesize a series of spiroindenoquinoxalines and spiroisatins based 2-pyrazolines.As a part of our ongoing research programs in the area of heterocyclic compounds containing nitrogen [62-69], herein, we report a novel **one-pot** procedure for synthesis of some new spiro indenoquinoxalines, indenopyridopyrazines and isatins based 2-pyrazolines in good yields, via condensation of chalcones and hydrazine in acidic condition.

Results and Discussion

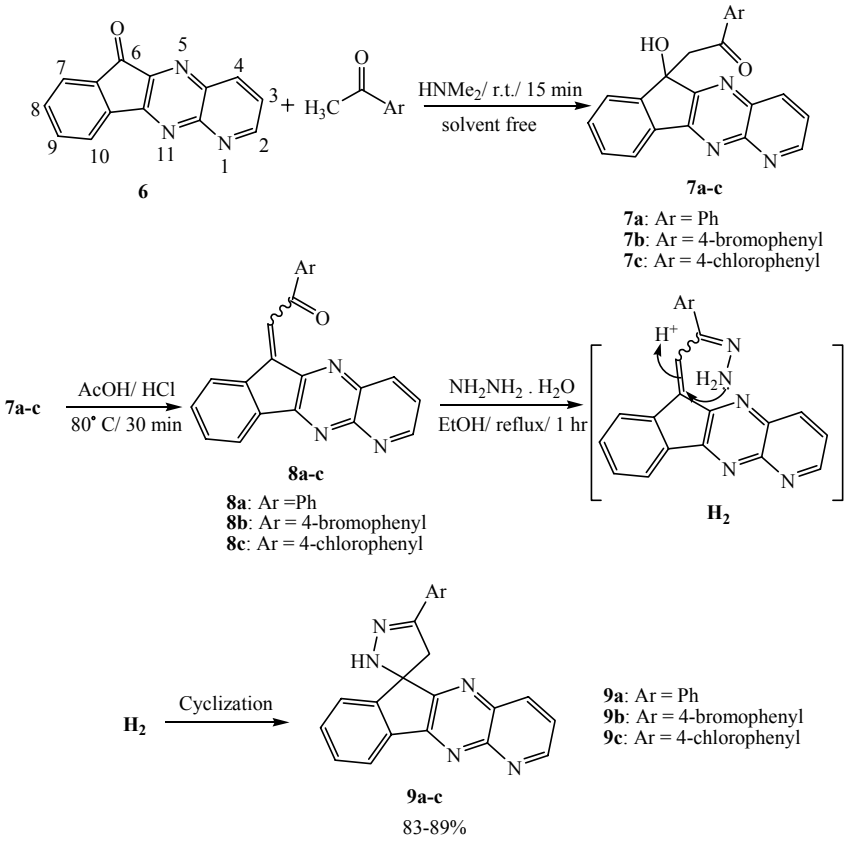
Many of 2-pyrazoline derivatives have been synthesized in last century,[70-72] but these synthesized spiro derivatives have not been reported yet. Therefore, our aim was to prepare some new spiro compounds with spiro 2-pyrazoline ring at C-11 carbon of indenoquinoxalines **1a-b**, C-6 carbon of indenopyridopyrazine **6** and C-3 carbon of isatin **10**, by the reaction of chalcones with hydrazines in **one-pot** rapid and efficient procedure.

The chalcones **4a-h, 8a-c** and **12a-c** were prepared by the reaction of acetophenones with indenoquinoxalines **1a-b**, indenopyridopyrazine **6** or isatin **10** in a solvent free condition under the influence of dimethylamine and then warming compounds **3a-h**, **7a-c** and **11a-c** in glacial acetic acid and HCl. Then the resulted chalcones were separated and allowed to react with hydrazine hydrate under refluxing in ethanol to afford spiro indenoquinoxaline-pyrazolines **5a-h**

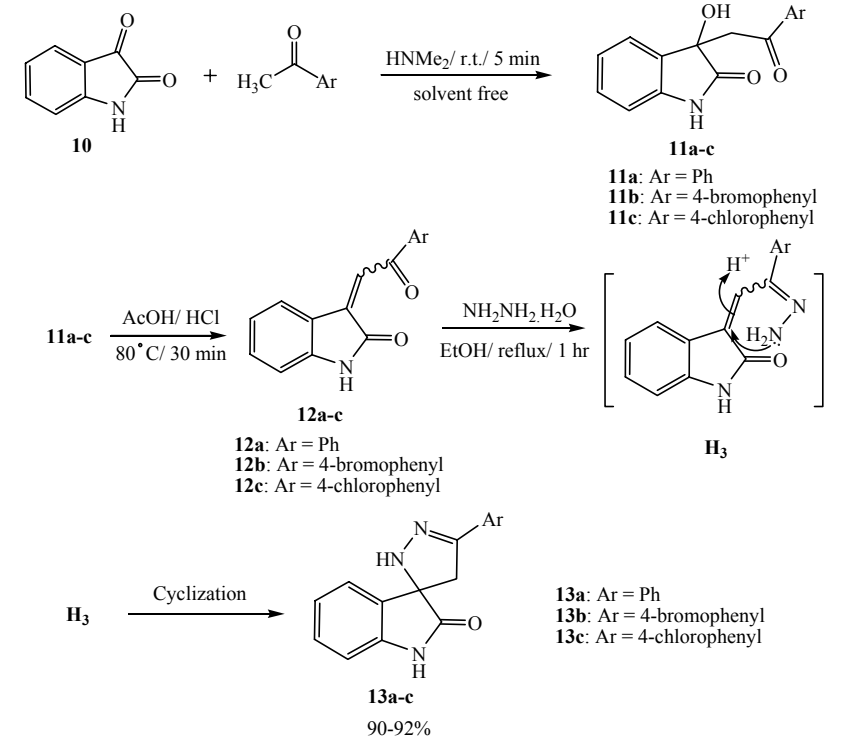
(Scheme 1), spiro indenopyridopyrazine-pyrazolines **9a-c** (Scheme 2) and spiro isatin-pyrazolines **13a-c** (Scheme 3) in good yields.



Scheme 1

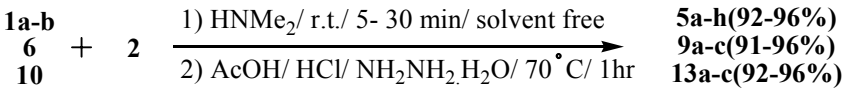


Scheme 2



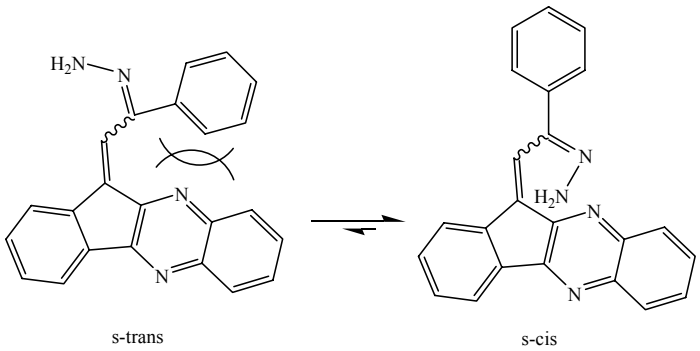
Scheme 3

In most methods chalcones were synthesized in base or acid catalyzed manner and the resulted chalcones were reacted with hydrazines after separation and purification. [44, 46-50, 54, 61, 76-77] In this work these spiro compounds also were made by **one-pot** procedure without isolation of the intermediate chalcones, and the reaction yield increased (Scheme 4).



Scheme 4

In the case of isatin the reaction rate was increased because the C=O group in 2 position of isatin increases the reactivity of carbon in 3 position by electron-withdrawing effect. The *s-trans* conformation of hydrazones $\mathbf{H_1}$, $\mathbf{H_2}$ and $\mathbf{H_3}$ involve a van der Waals repulsion between the rings of Ar and indenoquinoxaline (Scheme 5) and therefore the *s-cis* conformer must be the predominant conformer. [78]



Scheme 5

All prepared spiro compounds were purified by filtration and recrystallization of crude products from ethanol/water (70/30) solution.

The structures of compounds **5a-h**, **9a-c** and **13a-c** were deduced from their elemental analyses and their IR, ^{1}H-, ^{13}C- NMR and Mass spectroscopic measurements. All compounds have shown an excellent agreement between calculated and experimentally obtained data for CHN analysis. For example the ^{1}H-NMR spectrum of **5a** exhibited two doublets or AB quartet (δ 3.66 and 4.04) readily recognized to arise from two diastereotopic CH_2 protons of C-4 carbon of 2-pyrazoline ring along with multiplets (δ 7.43-8.17) for the aromatic protons. The singlet at 6.35 is related to NH. The ^{1}H decoupled ^{13}C-NMR spectrum of **5a** showed 21 distinct resonances in agreement with the proposed structure. Spiro carbon is resonated at δ 71.93 ppm and C=N carbon at 162.81 ppm.

In summary, the reaction described herein provides a simple and direct entry into a number interesting novel spiro indenoquinoxaline or isatin-based pyrazoline derivatives that may be of value in medicinal chemistry.

Experimental Section

General Procedures. Melting points were measured on an Electrothermal 9100 apparatus and are uncorrected. IR spectra were recorded as KBr pellets on Bomem FT-IR MB100 and Thermo Nicolet model Nexus 870 spectrometers. ^{1}H-NMR and ^{13}C-NMR spectra were determined on a Bruker DRX-300 Avance instrument in $CDCl_3$ using TMS as internal standard. Mass spectra were recorded on a Finnegan Mat magnetic sector model 8430 operating at an ionization potential of 70 eV, range 30-700 and 1 sec scanning. The purity of obtained spiro compounds was tested by the CHN analysis. Indenoquinoxalines **1a-b** were synthesized by the procedure of Ruhemann [73] and **6** by the method of Israel and co-workers [74]. The chalcones were synthesized on the basis of Lindwall and Mclennan method. [75]

Spiro indenoquinoxaline-pyrazolines (5a-h). To a solid homogenous mixture of 10 mmol indenoquinoxalines **1a-b** and 10 mmol acetophenones **2**, 10 drops of dimethylamine was added and the mixture stirred for 15-30 minutes and a colorless solid formed (**3a-h)**. 20 ml glacial acetic acid and five drops of concentrated HCl was added to this precipitate and the mixture warmed in 80 ºC for 30 minutes and after dehydration, chalcones **4a-h** were produced. These chalcones were allowed to react with hydrazine hydrate by two pathways. At first the chalcones were separated and after filtration washed with water (2×20ml) to remove acids and dimethylammonium acetate and then recrystallized from absolute ethanol. Then these chalcones were refluxed with 11 mmol hydrazine hydrate in 20 ml absolute ethanol for 1 hour to give corresponding spiro derivatives **5a-h** (Scheme 1). In second way or one-pot procedure the chalcones didn't separate and 11 mmol of hydrazine hydrate was added to the acidic solution of chalcone and reaction continued in 70-80 ºC for 1 hour and spiro compounds were formed in highly yields (Scheme 4).

5′-Phenyl-2′,4′-dihydrospiro[indeno[1,2-*b*]quinoxalin-11,3′-pyrazole] (5a). Yellow crystals, yield 83%, yield (one-pot) 94%, m.p. 243-245 ^{o}C; IR (KBr) cm^{-1}: 3257 (N-H), 1589 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.66 (1H, d, J = 18.0 Hz, 4-H$_a$), 4.04 (1H, d, J = 18.0 Hz, 4-H$_b$), 6.35 (1H, s, N-H), 7.43-8.17 (13H, m, Ar-H); ^{13}C- NMR (δ): 45.24, 71.93 (spiro carbon), 122.7, 124.2, 126.8, 129.1, 129.2, 129.4, 129.5, 129.6, 129.65, 130.1, 139.45, 130.5, 132.8, 133.2, 136.1, 143.2, 150.3, 151.9, 162.8 (**C**=N of pyrazoline ring); MS (m/z): 348 [M$^{+\cdot}$], 319, 271, 244, 231, 218, 105, 97, 83, 77, 43, 57; Anal. Calcd. for $C_{23}H_{16}N_4$ (348): C, 79.29; H, 4.63; N, 16.08. Found: C, 79.30; H, 4.61; N, 16.11%.

5′-(4-Bromophenyl)-2′,4′-dihydrospiro[indeno[1,2-*b*]quinoxalin-11,3′-pyrazole] (5b).Yellow crystals, yield 84%, yield (one-pot) 95%, m.p. 251-253 ^{o}C; IR (KBr) cm^{-1}: 3324 (N-H), 1585 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.64 (1H, d, J = 18.0 Hz, 4-H$_a$), 4.02 (1H, d, J = 18.0

Hz, 4-H_b), 6.31 (1H, s, N-H), 7.56-8.42 (12H, m, Ar-H); ^{13}C-NMR (δ): 45.0, 72.1 (spiro carbon), 123.05, 123.7, 124.2, 128.2, 129.2, 129.8, 130.1, 130.7, 131.7, 132.2, 133.4, 135.9, 142.7, 150.2, 150.7, 162.7 (**C**=N of pyrazoline ring); MS (m/z): M^+ group centered at 427, 398, 319, 231, 218, 183, 105, 77, 57, 43. Anal. Calcd. for $C_{23}H_{15}BrN_4$ (427): C, 64.65; H, 3.54; N, 13.11. Found: C, 64.57; H, 3.50; N, 13.19%.

5′-(4-Chlorophenyl)-2′,4′-dihydrospiro[indeno[1,2-*b*]quinoxalin-11,3′-pyrazole] (5c). Yellow crystals, yield 80%, yield (one-pot) 93%, m.p. 241-243 °C; IR (KBr) cm^{-1}: 3271 (N-H), 1595 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.64 (1H, d, J = 15.0 Hz, 4-H_a), 4.01 (1H, d, J = 15.0 Hz, 4-H_b), 6.32 (1H, s, N-H), 7.41-8.40 (12H, m, Ar-H); ^{13}C-NMR (δ): 45.1, 72.1 (spiro carbon), 123.6, 124.85, 128.0, 128.9, 129.3, 130.1, 130.8, 130.9, 131.2, 133.7, 135.7, 142.4, 147.0, 150.3, 150.7, 162.1 (**C**=N of pyrazoline ring); MS (m/z): 382 [$M^{+\cdot}$], 270, 242, 218, 105, 77, 71, 57, 43. Anal. Calcd. for $C_{23}H_{15}ClN_4$ (382): C, 72.16; H, 3.95; N, 14.63. Found: C, 72.16; H, 3.80; N, 14.72%.

5′-(4-Methoxyphenyl)-2′,4′-dihydrospiro[indeno[1,2-*b*]quinoxalin-11,3′-pyrazole] (5d). Yellow crystals, yield 89%, yield (one-pot) 95%, m.p. 234-236 °C; IR (KBr) cm^{-1}: 3259 (N-H), 1602 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.63 (1H, d, J = 18.0 Hz, 4-H_a), 3.88 (3H, s, OC**H$_3$**), 4.02 (1H, d, J = 18.0 Hz, 4-H_b), 6.20 (1H, s, N-H), 6.93-8.17 (12H, m, Ar-H); ^{13}C-NMR (δ): 45.46, 71.83 (spiro carbon), 55.8 (O**C**H$_3$), 114.5, 122.6, 124.2, 125.6, 128.3, 129.6, 130.1, 130.4, 130.45, 133.2, 136.2, 142.4, 143.4, 150.6, 151.9, 160.9 (**C**=N of pyrazoline ring); MS (m/z): 378 [M^+], 319, 231, 218, 183, 105, 77, 57, 43. Anal. Calcd. for $C_{24}H_{18}N_4O$ (378): C, 76.17; H, 4.79; N, 14.80. Found: C, 76.10; H, 4.88; N, 14.75%.

5′-(4-Nitrophenyl)-2′,4′-dihydrospiro[indeno[1,2-*b*]quinoxalin-11,3′-pyrazole] (5e). Orange-yellow crystals, yield 93%, yield (one-pot) 96%, m.p. 262-264 °C; IR (KBr) cm^{-1}: 3255 (N-H), 1591 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.68 (1 H, d, J = 15.0 Hz, 4-H_a), 4.04 (1 H, d, J = 15.0 Hz, 4-H_b), 5.66 (1H, s, N-H), 7.56-8.38 (12H, m, Ar-H); MS (m/z): 393 [$M^{+\cdot}$], 364, 318, 270, 232, 218, 105, 97, 77, 57, 43; Anal. Calcd. for $C_{23}H_{15}N_5O_2$ (393): C, 70.22; H, 3.84; N, 17.80. Found: C, 70.29; H, 3.71; N, 17.88%.

7,8-Dimethyl-5′-phenyl-2′,4′-dihydrospiro[indeno[1,2-*b*]quinoxalin-11,3′-pyrazole] (5f). Yellow crystals, yield 87%, yield (one-pot) 92%, m.p. 279-281 °C; IR (KBr) cm^{-1}: 3263 (N-H), 1594 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 2.49 (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.64 (1H, d, J = 18.0 Hz, 4-H_a), 4.01 (1H, d, J = 18.0 Hz, 4-H_b), 6.30 (1H, s, N-H), 7.43-8.20 (11H, m, Ar-H); ^{13}C-NMR (δ): 20.6, 20.7, 45.0 (**C**H$_2$), 72.1 (spiro carbon), 122.3, 123.9, 125.9, 127.95, 128.4, 128.45, 128.6, 128.7, 129.0, 130.0, 130.3, 131.1, 132.1, 132.3, 132.7, 139.9, 140.65, 141.8, 150.8, 161.4 (**C**=N of pyrazoline ring); Anal. Calcd. for $C_{25}H_{20}N_4$ (376): C, 79.76; H, 5.35; N, 14.88. Found: C, 79.74; H, 5.31; N, 14.85%.

5′-(4-Bromophenyl)-7,8-dimethyl-2′,4′-dihydrospiro[indeno[1,2-*b*]quinoxalin-11,3′-pyrazole] (5g). Light yellow crystals, yield 85%, yield (one-pot) 95%, m.p. 246-248 °C; IR (KBr) cm^{-1}: 3262 (N-H), 1585 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 2.49 (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.60 (1H, d, J = 18.0 Hz, 4-H_a), 3.97 (1H, d, J = 18.0 Hz, 4-H_b). 6.35 (1H, s, N-H), 7.50-8.15 (10H, m, Ar-H); ^{13}C-NMR (δ): 20.6, 20.7, 44.9 (**C**H$_2$), 72.1 (spiro carbon), 122.4,

124.1, 126.0, 128.2, 128.6, 128.7, 128.8, 128.85, 129.3, 130.1, 130.4, 131.4, 132.2, 132.4, 132.6, 140.12, 140.9, 142.2, 150.6, 162.2 (**C**=N of pyrazoline ring); Anal. Calcd. for $C_{25}H_{19}BrN_4$ (455): C, 65.94; H, 4.21; N, 12.30. Found: C, 65.93; H, 4.21; N, 12.32%.

5′-(4-Chlorophenyl)-7,8-dimethyl-2′,4′-dihydrospiro[indeno[1,2-*b*]quinoxalin-11,3′-pyrazole] (5h). Light yellow crystals, yield 87%, yield (one-pot) 93%, m.p. 240-242 °C; IR (KBr) /cm^{-1}: 3257 (N-H), 1588 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 2.49 (3H, s, CH_3), 2.52 (3H, s, CH_3), 3.60 (1H, d, J = 18.0 Hz, 4-H_a), 3.97 (1H, d, J = 18.0 Hz, 4-H_b). 6.32 (1H, s, N-H), 7/40-8/15 (10H, m, Ar-H); ^{13}C-NMR (δ): 20.6, 20.7, 44.95 (**C**H_2), 72.1 (spiro carbon), 122.4, 124.1, 126.1, 127.9, 128.2, 128.6, 128.8, 129.25, 129.3, 130.0, 130.5, 131.5, 132.3, 132.7, 140.2, 140.9, 142.2, 149.9, 161.6 (**C**=N of pyrazoline ring). Anal. Calcd. for $C_{25}H_{19}ClN_4$ (410): C, 73.08; H, 4.66; N, 13.63. Found: C, 73.03; H, 4.65; N, 13.59%.

Spiro indenopyridopyrazine-pyrazolines (9a-c). These spiro compounds were synthesized by the same procedures that used for compounds **5a-h**.

5′-Phenyl-2′,4′-dihydrospiro[indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6,3′-pyrazole] (9a). Light yellow crystals, yield 88%, yield (one-pot) 91%, m.p. 271-273 °C; IR (KBr)) /cm^{-1}: 3410 (N-H), 1611 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.69 (1H, d, J = 18.0 Hz, 4-H_a), 4.03 (1H, d, J = 18.0 Hz, 4-H_b). 6.30 (1H, s, N-H), 7.27–9.15 (12H, m, Ar-H); ^{13}C-NMR (δ): 45.3, 71.8 (spiro carbon), 122.8, 123.8, 124.25, 124.8, 125.6, 126.8, 129.0, 129.1, 129.7, 130.6, 130.9, 132.6, 134.15, 135.7, 137.5, 138.95, 150.8, 151.9, 152.5, 153.9, 157.15, 164.3 (**C**=N of pyrazoline ring); MS (m/z): 349 [$M^{+\cdot}$], 272, 219, 149, 109, 97, 85, 71), 57, 43. Anal. Calcd. for $C_{22}H_{15}N_5$ (349): C, 75.63; H, 4.33; N, 20.04. Found: C, 75.66; H, 4.34; N, 20.07%.

5′-(4-Bromophenyl)-2′,4′-dihydrospiro[indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6,3′-pyrazole] (9b). Light yellow crystals, yield 83%, yield (one-pot) 92%, m.p. 288-290 °C; IR (KBr)) /cm^{-1}: 3305 (N-H), 1611 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.66 (1H, d, J = 18.0 Hz, 4-H_a), 4.00(1H, d, J = 18.0 Hz, 4-H_b). 6.32 (1H, s, N-H), 7.57–9.15 (11H, m, Ar-H); ^{13}C-NMR (δ): 45.0, 71.9 (spiro carbon), 123.9, 124.2, 124.8, 128.2, 131.0, 131.55, 132.3, 134.2, 135.8, 137.5, 139.0, 150.5, 150.7, 152.5, 153.9, 164.1 (**C**=N of pyrazoline ring); MS (m/z): M^+ group centered at 428, 379, 271, 237, 219, 185, 157, 102, 85, 71, 57, 43, 36. Anal. Calcd. for $C_{22}H_{14}BrN_5$ (428): C, 61.70; H, 3.29; N, 16.35. Found: C, 61.73; H, 3.22; N, 16.31%.

5′-(4-Chlorophenyl)-2′,4′-dihydrospiro[indeno[1,2-*b*]pyrido[3,2-*e*]pyrazin-6,3′-pyrazole] (9c). Light yellow crystals, yield 89%, yield (one-pot) 94%, m.p. 260-262 °C; IR (KBr)) /cm^{-1}: 3302 (N-H), 1609 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.66 (1H, d, J = 18.0 Hz, 4-H_a), 4.00(1H, d, J = 18.0 Hz, 4-H_b). 6.32 (1H, s, N-H), 7.41–9.15 (11H, m, Ar-H); ^{13}C-NMR (δ): 45.1, 71.9 (spiro carbon), 120.3, 123.7, 123.85, 124.2, 124.6, 124.8, 128.0, 129.0, 129.3, 130.95, 131.1, 132.95, 134.15, 135.8, 137.5, 138.3, 138.9, 150.5, 150.7, 153.3, 154.0, 164.1 (**C**=N of pyrazoline ring); MS (m/z): 383 [$M^{+\cdot}$], 271, 246, 219, 139, 111, 97, 85, 71, 57, 43. Anal. Calcd. for $C_{22}H_{14}ClN_5$ (383): C, 68.84; H, 3.68; N, 18.25. Found: C, 68.79; H, 3.59; N, 18.21%.

Spiro isatin-pyrazolines (13a-c). Spiro isatin-pyrazolines **13a-c** were prepared corresponding to the methods applied for previous spiro derivatives.

5′-Phenyl-2′,4′-dihydrospiro[indol-3,3′-pyrazol]-2(1*H*)-one (13a). colorless crystals, yield 89%, yield (one-pot) 95%, m.p. 200-202 °C; IR (KBr)) /cm^{-1}: 3479 (N-H of isatin), 3272 (N-H of pyrazoline), 1701 (C=O), 1613 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.43 (1H, d, *J* = 15.0 Hz, 4-H$_a$), 3.72 (1H, d, *J* = 15.0 Hz, 4-H$_b$), 6.20 (1H, s, N-H of pyrazoline), 6.92–8.00 (9H, m, Ar-H) , 9.16 (1H, brs, N-H of isatin); ^{13}C-NMR (δ): 45.1, 70.3 (spiro carbon), 111.0, 123.7, 126.8, 128.3, 128.4, 129.0, 129.1, 129.7, 130.1, 130.3, 132.3, 132.5, 140.4, 151.1 (**C**=N of pyrazoline ring),180.3 (**C**=O). Anal. Calcd. for $C_{16}H_{13}N_3O$ (263): C, 72.99; H, 4.98; N, 15.96. Found: C, 72.87; H, 5.02; N, 15.93%.

5′-(4-Bromophenyl)-2′,4′-dihydrospiro[indol-3,3′-pyrazol]-2(1*H*)-one (13b). colorless crystals, yield 86%, yield (one-pot) 93%, m.p. 237-239 °C; IR (KBr)) /cm^{-1}: 3467 (N-H of isatin), 3292 (N-H of pyrazoline), 1704 (C=O), 1619 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.42 (1H, d, *J* = 15.0 Hz, 4-H$_a$), 3.58 (1H, d, *J* = 15.0 Hz, 4-H$_b$), 6.36 (1H, s, N-H of pyrazoline), 6.92–7.68 (8H, m, Ar-H) , 9.32 (1H, brs, N-H of isatin); ^{13}C-NMR (δ): 44.1, 70.2 (spiro carbon), 110.1, 122.9, 124.0, 128.05, 129.7, 131.9, 132.7, 141.8, 147.5 (**C**=N of pyrazoline ring), 179.4 (**C**=O). Anal. Calcd. for $C_{16}H_{12}BrN_3O$ (342): C, 56.16; H, 3.53; N, 12.28. Found: C, 56.08; H, 3.59; N, 12.20%.

5′-(4-Chlorophenyl)-2′,4′-dihydrospiro[indol-3,3′-pyrazol]-2(1*H*)-one (13c). colorless crystals, yield 89%, yield (one-pot) 92%, m.p. 222-224 °C; IR (KBr)) /cm^{-1}: 3461 (N-H of isatin), 3279 (N-H of pyrazoline), 1712 (C=O), 1609 (C=N of pyrazoline ring); ^{1}H-NMR (δ): 3.43 (1H, d, *J* = 15.0 Hz, 4-H$_a$), 3.58 (1H, d, *J* = 15.0 Hz, 4-H$_b$), 6.33 (1H, s, N-H of pyrazoline), 6.92–7.75 (8H, m, Ar-H) , 9.32 (1H, brs, N-H of isatin); ^{13}C-NMR (δ): 44.1, 70.1, 110.05, 110.1, 122.85, 124.0, 127.8, 128.9, 129.7, 132.3, 133.9, 141.7, 147.5 (**C**=N of pyrazoline ring), 178.55 (**C**=O). Anal. Calcd. for $C_{16}H_{12}ClN_3O$ (297): C, 64.54; H, 4.06; N, 14.11. Found: C, 64.47; H, 4.02; N, 14.01%.

Acknowledgements

We gratefully acknowledge the financial support from the Research Council of Science and Research Campus Islamic Azad University.

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