Ionic Liquid Mediated Green Synthesis of Spirooxindoles from *N*-methyl Quinolones and Their Anti Bacterial Activity

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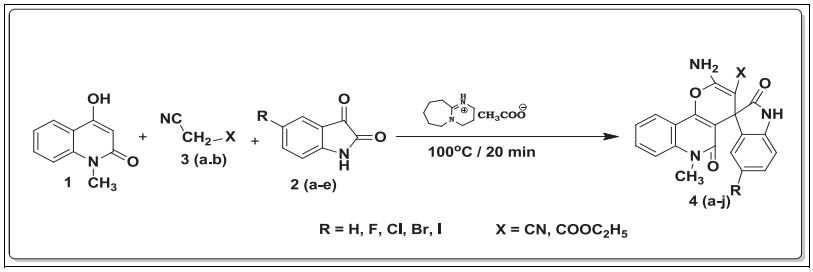
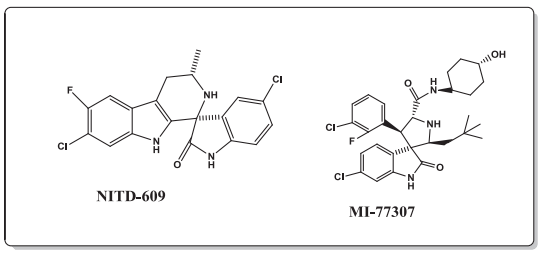


Three-component reaction involving condensation of 1-methyl quinoline-2,4(1*H*,3*H*)-dione **1**, isatins **2(a–e)**, and malononitrile/cyanoacetic ester **3(a–b)** in the task-specific ionic liquid [DBU][Ac] (1,8-diazabicyclo[5.4.0]-undec-7-en-8-ium acetate) leading to the spirooxindole derivatives **4(a–j)** is described. This approach is affords the products in high yields without use of column chromatography and resulting compounds were evaluated for antibacterial activity against both gram positive and gram negative bacteria (*Staphylococcus aureus, Escherichia coli, Bacillus cereus, Bacillus subtilis, Salmonella typhimurium, and Klebsiella pneumonia*). Among the all compounds, four compounds, that is, **4b, 4e, 4f, 4g, 4j** exhibited moderate activity against all the strains as compared with the standard used.

INTRODUCTION

The spirooxindole system, probably most well-known heterocycle, a common and important feature of a variety of natural products [1] and medicinal agents. Spiro compounds represent an important class of naturally occurring substances characterized by highly pronounced biological properties [2]. The spirooxindole system is a core structure of many pharmacological agents and natural alkaloids such as gelsemine [3], horsfiline [4], mitraphylline [5], spirotryprotatins [6] A, B, and others [7]. Especially spirooxindoles acts as antibacterial [8], anti-viral [9], and anti-fungal agents [10]. These are the great interest in modern organic, medicinal and natural product chemistry. In this connection, spirooxindoles with diverse pharmacological activities have gained much interest because of its well-defined three dimensional stereo-architecture [11]. Because of the presence of conformational restrictions of spirooxindoles and spirocarbon causes structural rigidity that triggers the biological activities [12], that is, NITD 609 [13] used in malarial treatment and MI77301 [14] used for cancer therapy. Recently, Zhu et al. [15] reported three component Triethylbenzylammonium Chloride (TEBA) catalyzed syntheses of spirooxindoles in aqueous medium. And Shanthi et al. [16] reported $InCl_3$ mediated spirooxindoles under solvent free conditions by using microwave method and Shaghyegh et al. [17] reported quinolone substituted spirooxindoles from one-pot method under ultrasonic conditions. The need to reduce the amount of toxic waste and by product formation from chemical process is increasing in the designing process of synthetic methods.



One of the most promising approaches is using ionic liquids as reaction media. Ionic liquids are the salts of organic heterocyclic cations and inorganic anions. They exist in liquid state at ambient temperatures; hence, the reactions in the presence of ionic liquids need no additional solvent. Ionic liquids have attracted much attention because of their mild reaction conditions, short

reaction times and better yield, solvating ability, and easy recyclability. Various reactions have been reported recently using ionic liquids as a catalyst, reaction media, as rate enhancers, and in peptide synthesis [18].

RESULTS AND DISCUSSION

A mixture of 1-methylquinoline-2,4(1*H*,3*H*)-dione **1**, isatin **2(a–e)**, malononitrile or ethyl cyanoacetate **3(a–b)** were stirred at 100°C for 20 min in DBU acetate. After processing, the product 2′-amino-6′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]quinoline]-3′-carbonitrile **4(a–j)** was isolated and characterized by IR, ^{1}HNMR,^{13}C–NMR, and mass spectral data. (For details please see the Experimental Section). When the reaction was carried out in the absence of DBU acetate by refluxing the reactants in ethanol for 2–3 h, no progress in the product formation was observed by periodic thin-layer chromatography (TLC) analysis of the reaction mixture.

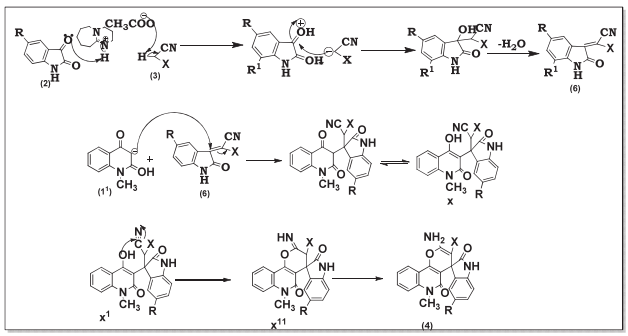
Initially a mixture of 1-methylquinoline-2,4(1*H*,3*H*)-dione **1,** isatin **2a**, malononitrile **3a**, and was stirred with 5 mL of [DBU] [Ac] at room temperature. TLC showed no formation of the product. Therefore, the same mixture was heated at 100°C for 20 min to accomplish the reaction. After workup, spirooxindole was the only product isolated in high yield. We noticed that reducing the quantity of [DBU] [Ac] (3 mL) did not affect the yields. However, when the multi component reaction was carried out independently with DBU free base as catalyst in ethanol solution, the reaction was found to be very sluggish as observed by TLC, leading to the poor yields of the final product on processing the reaction mixture after 3 h (Scheme 1).

The catalyst/reaction medium plays a vital role in determining the success of the reaction in terms of rate and yields. Various ionic liquids such as [bmim]Br, [bmim]$AlCl_4$, [bmim]SbF_6, [bmim]PF_6,[DBU][Lac] and DBU were screened, apart from DBU acetate, for the synthesis of spirooxindoles. Among these ionic liquids, DBU acetate proved to be the most effective as far as completion of reaction in short time and yields are concerned (Table 1). As shown in the Chart 1, the ionic liquid [DBU] [Ac] could be recycled four times without considerable loss of activity.

In order to demonstrate the scope of these conditions, several examples were studied and are summarized in Table 2. In all cases, the three-component reaction proceeded smoothly to give the corresponding spirooxindoles in high yields. As shown in the Table 2, it was found that this method works with a wide variety of substrates.

The synthesis of spirooxindoles could also be achieved in two different methods in a tandem fashion (Scheme 2). Thus, a mixture of **2a**, **3a,** and DBU acetate was stirred at 100°C for 20 min. The reaction was monitored by TLC. After the completion of the reaction, as shown by disappearance of one of the reactants, to the resulting mixture, **1** was added and the resulting mixture stirred at 100°C for further 20 min. At the end of this period, the mixture was processed to obtain **4a** as final product. Similarly, a mixture of **2a**, **1,** and DBU acetate was stirred at 100°C for 20 min. The reaction was monitored by TLC. After the completion of reaction, as shown by disappearance of one of the reactants to the resulting mixture, **3a** was added and the whole mixture stirred at RT for further 20 min. At the end of this period, the mixture was processed to obtain the final **4a**.

Mechanism I.



Plausible mechanism for the formation of spirooxindoles 4 (a–j):. Two possible mechanisms have been proposed for the formation of **4** from **1, 2(a–e)** and **3(a,b).**

Scheme 1. Synthesis of **4(a–j)** from **1, 2(a–e)**, and **3(a–b)**.

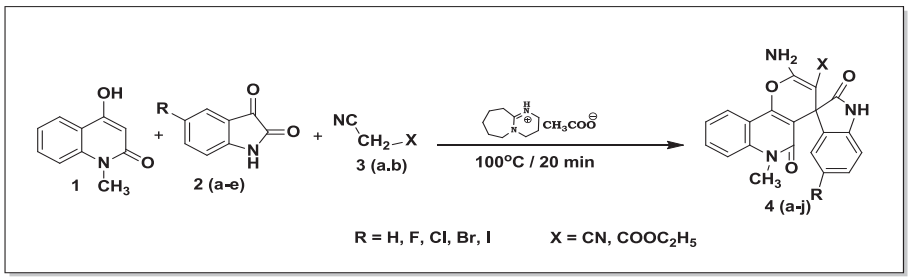


Table 1

Ionic liquids screened for the synthesis of spirooxindoles.

Entry	Ionic liquid used	Time (min) of reaction	Temp (°C)	Yield (%) of product 4a
1	[bmim]Br	90	100	32
2	[bmim]$AlCl_4$	90	100	55
3	[bmim]SbF_6	90	100	45
4	[bmim]PF_6	90	100	50
5	**[DBU][AC]**	**20**	**100**	**92**
6	[DBU][Lac]	30	100	75
7	DBU	40	100	30

Bold symbols indicates [DBU][AC] gave high yield than other ionic liquids.

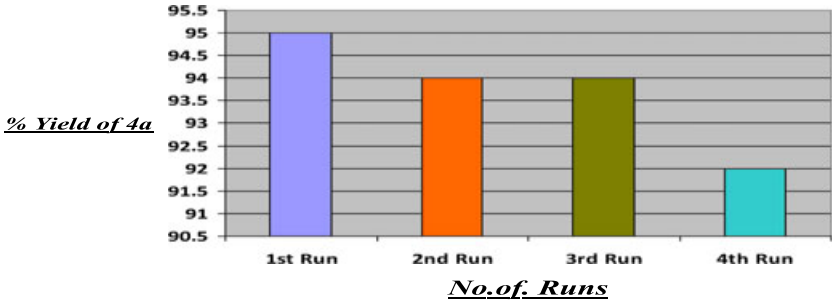


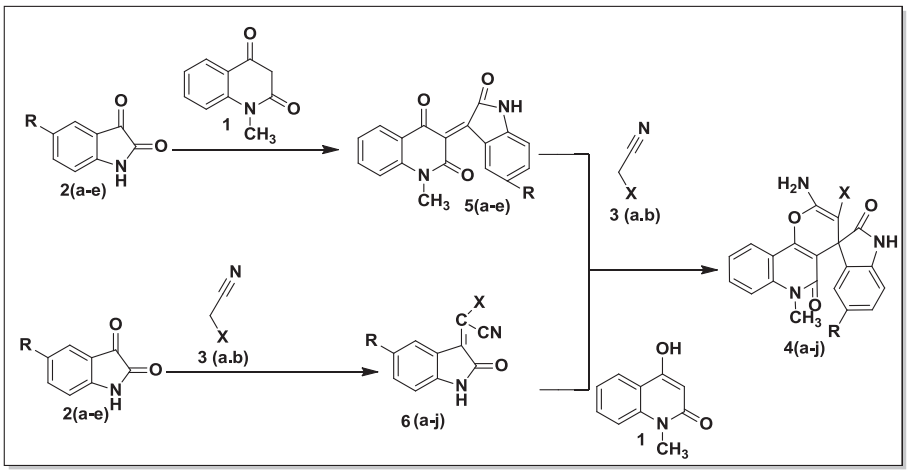
Chart 1. Reaction of **1**, **2a**, and **3a** in DBU acetate at 100oC for 20 min. [Color figure can be viewed at wileyonlinelibrary.com]

Table 2

Synthesis of spirooxindole derivatives 4(a–j) from 1, 2 and 3.

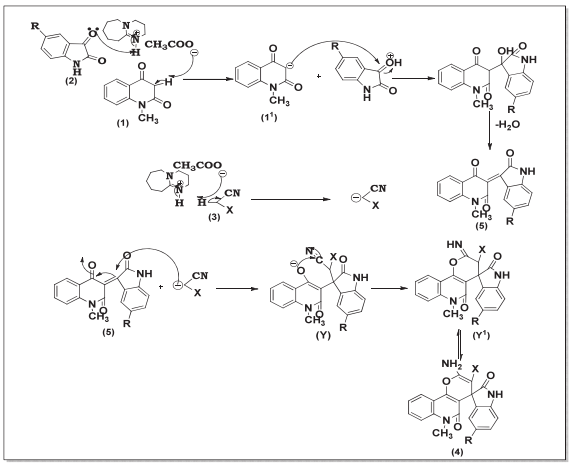
S.No	Isatin (2)	Active methylene (3)	Product	Time (min)	Yield (%)
1	2a(R = H)	3a (X = CN)	4a	15	92
2	2b (R = F)	3a (X = CN)	4b	18	88
3	2c (R = Cl)	3a (X = CN)	4c	20	85
4	2d (R = Br)	3a (X = CN)	4d	17	90
5	2e (R = I)	3a (X = CN)	4e	20	94
6	2a (R = H)	3b (X = $COOC_2H_5$)	4f	18	90
7	2b (R = F)	3b (X = $COOC_2H_5$)	4g	20	87
8	2c (R = Cl)	3b (X = $COOC_2H_5$)	4h	20	88
9	2d (R = Br)	3b (X = $COOC_2H_5$)	4i	20	86
10	2e (R = I)	3b (X = $COOC_2H_5$)	4j	20	90

Scheme 2. Alternate synthesis of Spirooxindoles.



In the first mechanism proposed, the reaction involves a Knoevenagel condensation catalyzed by DBU acetate between isatin **2** and active methylene group of the cyano derivative **3a** to yield an α, β-unsaturated nitrile intermediate **6**. The latter is then attacked by the carbanion of the 1-methylquinoline-2,4(1*H*,3*H*)-dione compound **1**[1]in the form of Michael addition followed by a keto-enol tautomerization to furnish the enol intermediate **X**. Nucleophilic addition of the hydroxyl group of intermediate **X** to the cyano moiety afforded imine intermediate **X**[I], which undergoes enolisation to yield the final product **4**.

Mechanism II.



In the second mechanism, the acetate ion abstracts the proton from the active methylene group of **1** to afford carbanion species **1**[I], which attacks the protonated carbonyl group of the isatin to result in a C–C bond intermediate. Loss of water molecule gives the α, β-unsaturated diketo intermediate **5.** The latter is then attacked by the carbanion of the **3** to afford **Y,** which undergoes intramolecular nucleophilic attack by hydroxyl group on the cyano afforded imine intermediate **Y**[1], which undergoes enolisation to yield the final product **4**. (Table 3–6).

ANTIBACTERIAL ASSAY

The antibacterial activity of all the synthesized spirooxindole derivatives **4(a–j)** was determined using the well disc diffusion method [19] against different gram positive and gram negative microbial strains, which were produced from the Microbial Culture Collection Department of Chemistry, JNTU-Hyderabad, India. The clinical strains were seeded on the surface of the media Petri plates, containing Muller-Hinton agar with 0.1 mL of prepared microbial suspensions, which individually containing 1.5×10^8 cfu mL^{-1}. Wells of 6.0 mm diameter were prepared in the media plates by using a cork borer and the synthesized compounds dissolved in 15% DMSO at a dosage range of 250 μg/disc, was performed in order to evaluate the inhibitory potency of the compounds against seven pathogenic bacterial strains namely *Staphylococcus aureus, Escherichia coli, Bacillus cereus, Bacillus subtilis, Salmonella typhimurium, and Klebsiella pneumonia*. Out of all the spirooxindole derivatives four compounds, that is, **4b, 4e, 4f, 4g, 4j** exhibited moderate activity against all the tested strains with zone of inhibition between 10 and 16 mm and minimum inhibitory concentration value in the range of 75–170 μg/mL when compared with the standard gentamicin, all the results were summarized in Table 7.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The progress of the reaction was monitored by TLC performed on silica gel G coated Merck plastic sheets and spots were observed by exposure to iodine vapor or UV light. IR spectra were recorded by using KBr disc on a Perkin-Elmer 240c analyzer. ^{1}H NMR spectra were recorded on Brucker DPX-400 at 400 MHz (chemical shifts in δ, ppm) and Mass spectra on an Agilent liquid chromatography–mass spectrometry instrument giving only M+ values in Q + 1 mode.

General procedure for synthesis of spirooxindoles 4(a–j). A mixture of **1**(1 mmol), **2a–e** (1 mmol), **3a** or **3b** (1 mmol) respectively in DBU acetate (3 mL) was stirred at 100°C for 20 min. To the resulting oily reaction mixture was added 5 mL of ethanol to force out the crude product from the polar ionic liquid reaction medium. Then the precipitated product was filtered and washed with cold ethanol to afford the pure products. The collected ionic liquid along with ethanol as filtrate in the filtration flask was evaporated to remove ethanol and the obtained ionic liquid was reused for subsequent reactions.

Table 3

Synthesis of 5 (a–e) from 2(a–e) and 1.

S. No	Isatin (2)	Product 5(a–e)	Time (min)	Yield (%)
1	2a (R = H)	5a	20	87
2	2b (R = F)	5b	22	81
3	2c (R = Cl)	5c	20	83
4	2d (R = Br)	5d	20	83
5	2e (R = I)	5e	20	85

Table 4

Synthesis of 6(a–j) from 2(a–e) and 3(a, b).

S. No	Isatin (2)	Active methylene (3)	Product 6(a–j)	Time (min)	Yield (%)
1	2a (R = H)	3a (X = CN)	6a	20	89
2	2b (R = F)	3a (X = CN)	6b	23	80
3	2c (R = Cl)	3a (X = CN)	6c	21	81
4	2d (R = Br)	3a (X = CN)	6d	20	81
5	2e (R = I)	3a (X = CN)	6e	20	83
6	2a (R = H)	3b (X = $COOC_2H_5$)	6f	20	87
7	2b (R = F)	3b (X = $COOC_2H_5$)	6g	24	79
8	2c (R = Cl)	3b (X = $COOC_2H_5$)	6h	22	82
9	2d (R = Br)	3b (X = $COOC_2H_5$)	6i	20	82
10	2e (R = I)	3b (X = $COOC_2H_5$)	6j	21	84

Table 5

Synthesis of 4(a–j) from 5(a–e) and 3(a, b).

S. No	5(a–e)	3 (a–b)	Product	Time (min)	Yield (%)
1	5a(R = H)	3a (X = CN)	4a	14	90
2	5b (R = F)	3a (X = CN)	4b	20	86
3	5c (R = Cl)	3a (X = CN)	4c	18	86
4	5d (R = Br)	3a (X = CN)	4d	18	88
5	5e (R = I)	3a (X = CN)	4e	17	87
6	5a (R = H)	3b (X = $COOC_2H_5$)	4f	16	89
7	5b (R = F)	3b (X = $COOC_2H_5$)	4g	20	85
8	5c (R = Cl)	3b (X = $COOC_2H_5$)	4h	18	87
9	5d (R = Br)	3b (X = $COOC_2H_5$)	4i	20	87
10	5e (R = I)	3b (X = $COOC_2H_5$)	4j	19	89

Table 6

Synthesis of 4(a–j) from 6(a–j) and 1.

S. No	6(a–j)	Product	Time (min)	Yield (%)
1	6a	4a	16	87
2	6b	4b	21	81
3	6c	4c	20	85
4	6d	4d	18	86
5	6e	4e	16	87
6	6f	4f	18	80
7	6g	4g	22	85
8	6h	4h	20	86
9	6i	4i	20	87
10	6j	4j	19	87

To compensate for the loss of some acetic acid during the work up procedure, an amount acetic acid (2 mL) was added after each run. A volume of DBU (2 mL) was added to the ionic liquid filtrate after three runs.

4a (R = H, X = CN): 2′-amino-6′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline 3,4′pyrano [3,2-c]quinoline]-3′-carbonitrile. Yield: 92%; MP: >300°C; IR (KBr): 3499, 3326 (unequal doublet, asymmetric, and symmetric stretchings of $-NH_2$), 2190 (sharp, medium, −CN), 1720, 1674 cm^{-1} (−CO-group, broad); ^{1}H-NMR(DMSO d_6/TMS): δ 3.47 (s, 3H, $-NCH_3$), 6.80 (s, 2H, $-NH_2$), 6.85–8.06 (m, 7H, Ar-H), 10.51 (s, 1H, −NH, D_2O exchangeable). ^{13}C-NMR (DMSO d_6/TMS): δ 29.1, 48.1,

Table 7

Zone of inhibition of active compounds **4b, 4e, 4f, 4g, 4j** against pathogenic bacterial test strains using gentamicin as positive control.

S. NO	Test compounds	*B. cereus*	*B. subtilis*	*S. aureus*	*E. coli*	*K. pneumoniae*	*S. typhimurium*	*P. aeruginosa*
1	4a	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	**4b**	12.66	12.02	13.35	11.31	11.00	11.01	11.67
3	4c	10.00	10.00	0.00	0.00	10.00	0.00	0.00
4	4d	10.00	10.00	0.00	0.00	10.00	0.00	0.00
5	**4e**	13.67	11.65	13.68	11.35	11.02	11.34	14.66
6	**4f**	13.67	11.34	14.32	10.69	11.00	11.04	13.36
7	**4g**	13.68	13.04	13.00	12.38	12.38	12.68	13.67
8	4h	0.00	0.00	0.00	0.00	0.00	0.00	0.00
9	4i	10.00	10.00	0.00	0.00	10.00	0.00	0.00
10	**4j**	14.00	13.38	14.37	13.32	13.10	13.37	15.62
11	**Gentamicin**	30.34	30.69	30.02	30.23	29.34	30.00	29.37

Bold text indicates high activity than other derivatives.

57.2, 106.4, 109.1, 112.2, 114.9, 117.3, 121.6, 122.3, 123.3, 128.2, 132.1, 134.2, 138.6, 142.4, 151.4, 158.7, 158.8, 177.7; m/z (M^++1): 371. *Anal.* Calcd for $C_{21}H_{14}N_4O_3$ (370.12): C, 68.50; H, 3.81; N, 15.13% Found: C, 68.54; H, 3.85; N, 15.17%.

4b (R = F, X = CN): 2′-amino-5-fluoro-6′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline 3,4′-pyrano[3,2-c]quinoline]-3′-carbonitrile. Yield: 88%; Time: 8 min; MP: >300°C; IR (KBr): 3482, 3332 (unequal doublet, asymmetric, and symmetric stretchings of $-NH_2$), 2182 (sharp, medium, −CN), 1722, 1672 cm^{-1} (−CO-group, broad); ^{1}H-NMR(DMSO d_6/TMS): δ 2.78 (s, 3H, $-NCH_3$), 6.86 (s,2H, $-NH_2$), 6.75–7.60 (m, 7H,Ar-H), 10.15 (s, 1H, −NH, D_2O exchangeable).^{13}C-NMR (DMSO d_6/TMS): δ 29.3, 48.4, 57.1, 106.6, 109.3, 112.6, 114.8, 117.4, 121.3, 122.6, 123.6, 128.4, 132.0, 134.5, 138.8, 142.2, 151.1, 158.3, 158.9, 177.3; m/z (M^++1): 389. *Anal.* Calcd for $C_{21}H_{13}FN_4O_3$ (388.12): C, 64.95; H, 3.37; N, 14.43; F, 4.89% Found: C, 64.98; H, 3.33; N, 14.48; F, 4.84%.

4c (R = Cl, X = CN): 2′-amino-5-chloro-6′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]quinoline]-3′-carbonitrile. Yield: 85%; Time: 10 min; MP: >280°C; IR (KBr): 3489, 3336 (unequal doublet, asymmetric, and symmetric stretchings of −NH2), 2229 (sharp, medium, −CN), 1721, 1672 cm^{-1} (−CO-group, broad); ^{1}H-NMR(DMSO d_6/TMS): δ 2.65 (s, 3H, $-NCH_3$), 6.91 (s, 2H, $-NH_2$), 7.05–7.59 (m, 7H,Ar-H), 10.23 (s, 1H, −NH, D_2O exchangeable).^{13}C-NMR (DMSO d_6/TMS): δ 29.4, 48.5, 57.4, 106.9, 109.3, 112.7, 114.3, 117.2, 121.7, 122.8, 123.2, 128.1, 132.8, 134.2, 138.3, 142.1, 151.7, 158.0, 158.2, 177.1; m/z (M^++1): 405. *Anal.* Calcd for $C_{21}H_{13}ClN_4O_3$ (404.21): C, 62.31; H, 3.24; N, 13.84; Cl, 8.76% Found: C, 62.34; H, 3.20; N, 13.88; Cl, 8.72%.

4d (R = Br, X = CN): 2′-amino-5-bromo-6′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]quinoline]-3′-carbonitrile. Yield: 90%; Time: 7 min; MP: >300°C; IR (KBr): 3487, 3322 (unequal doublet, asymmetric, and symmetric stretchings of $-NH_2$), 2180 (sharp, medium, −CN), 1719, 1670 cm^{-1} (−CO-group, broad); ^{1}H-NMR(DMSO d_6/TMS): δ 2.70 (s, 3H, $-NCH_3$), 7.02 (s, 2H, $-NH_2$), 6.95–7.70 (m, 7H, Ar-H), 10.12 (s, 1H, −NH, D_2O exchangeable). ^{13}C-NMR (DMSO d_6/TMS): δ 29.1, 48.9, 57.7, 106.0, 109.6, 112.9, 114.2, 117.8, 121.9, 122.2, 123.9, 128.9, 132.9, 134.1, 138.3, 142.9, 151.0, 158.1, 158.7, 177.8; m/z (M^++1): 449. *Anal.* Calcd for $C_{21}H_{13}BrN_4O_3$ (448.02): C, 56.14; H, 2.92; N, 12.47; Br, 17.79% Found: C, 56.18; H, 2.96; N, 12.43; Br, 17.73%.

4e (R = I, X = CN): 2′-amino-5-iodo-6′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]quinoline]-3′-carbonitrile. Yield: 94%; Time: 10 min; MP: >300°C; IR (KBr): 3479, 3198 (unequal doublet, asymmetric, and symmetric stretchings of $-NH_2$), 2205 (sharp, medium, −CN), 1720, 1673 cm^{-1} (−CO-group, broad); ^{1}H-NMR (DMSO d_6/TMS): δ 2.65 (s, 3H, $-NCH_3$), 6.96 (s, 2H, $-NH_2$), 6.85–7.64 (m, 7H, Ar-H), 10.09 (s, 1H, −NH, D_2O exchangeable). ^{13}C-NMR (DMSO d_6/TMS): δ 29.3, 48.2, 57.9, 106.2, 109.4, 112.8, 114.7, 117.2, 121.1, 122.8, 123.2, 128.2, 132.1, 134.4, 138.2, 142.8, 151.2, 158.2, 158.5, 177.2; m/z (M^++1): 497. *Anal.* Calcd for $C_{21}H_{13}IN_4O_3$ (496.04): C, 50.83; H, 2.64; N, 11.29; I, 25.57% Found: C, 50.87; H, 2.61; N, 11.24; I, 25.55%.

4f (R = H, X = $COOC_2H_5$): ethyl 2′-amino-6′-methyl-2,5′-dioxo-5′,6′-dihydrospiro[indoline-3,4′-pyrano[3,2-c]quinoline]-3′-carboxylate. Yield: 92%; MP: >300°C; IR (KBr): 3374, 3253 (unequal doublet, asymmetric, and symmetric stretchings of $-NH_2$), 2199 (sharp, medium, −CN), 1698, 1656, 1630 cm^{-1} (−CO-group, broad); ^{1}H-NMR (DMSO d_6/TMS): δ 0.82 (t, 3H, CH_3), 3.7 (s, 3H, $-NCH_3$), 4.43 (q, 2H, $-CH_2$), 6.6 (s, 2H, $-NH_2$), 6.76–8.1 (m, 7H, Ar-H), 10.22 (s, 1H, −NH, D_2O exchangeable). ^{13}C-NMR (DMSO d_6/TMS): δ 13.1, 29.1, 47.9, 58.9, 76.0, 108.0, 109.0, 112.2, 114.7, 120.5, 122.1, 122.5, 127.3, 132.0, 135.5, 138.4, 144.6, 150.2, 158.6, 159.1, 167.5, 179.6; m/z (M^++1): 418. *Anal.* Calcd for $C_{23}H_{19}N_3O_5$ (417.21): C, 66.18; H, 4.59, N, 10.47% Found: C, 66.15; H, 4.56, N, 10.44%.

4g (R = F, X = $COOC_2H_5$): ethyl 2′-amino-5-fluoro-6′-methyl-2,5′-dioxo-5′,6’dihydrospiro [indoline-3,4′-pyrano[3,2-c]quinoline]-3′-carboxylate. Yield: 87%; Time: 7 min; MP: 184–186°C; IR (KBr): 3380, 3246 (unequal doublet, asymmetric, and symmetric stretchings of $-NH_2$), 2187 (sharp, medium, −CN), 1687, 1664, 1654 cm^{-1} (−CO-group, broad); ^{1}H-NMR (DMSO d_6/TMS): δ 0.98 (t, 3H, CH_3), 3.8(s, 3H, $-NCH_3$), 4.56 (q, 2H, $-CH_2$), 6.7 (s, 2H, $-NH_2$), 6.79–8.3 (m, 7H, Ar-H), 10.24 (s, 1H, −NH, D_2O exchangeable). ^{13}C-NMR (DMSO d_6/TMS): δ 13.1, 29.1, 47.9, 58.9, 76.0, 108.0, 109.0, 112.2, 114.7, 120.5, 122.1, 122.5, 127.3, 132.0, 135.5, 138.4, 144.6, 150.2, 158.6, 159.1, 167.5, 179.6; m/z (M^++1): 436. *Anal.* Calcd for $C_{23}H_{18}FN_3O_5$ (433.01): C, 63.45; H, 4.17; N, 9.65; F, 4.36% Found: C, 63.49; H, 4.13; N, 9.69; F, 4.32%.

4h (R = Cl, X = $COOC_2H_5$): ethyl 2′-amino-5-chloro-6′-methyl-2,5′-dioxo-5′,6’dihydrospiro [indoline-3,4′-pyrano[3,2-c]quinoline]-3′-carboxylate. Yield: 88%; Time: 8 min; MP: 268–70°C; IR (KBr): 3372, 3250 (unequal doublet, asymmetric, and symmetric stretchings of $-NH_2$), 2197 (sharp, medium, −CN), 1697, 1650, 1628 cm^{-1} (−CO-group, broad); ^{1}H-NMR (DMSO d_6/TMS): δ 0.96 (t, 3H, CH_3), 3.4(s, 3H, $-NCH_3$), 4.65 (q, 2H, $-CH_2$), 6.4 (s, 2H, $-NH_2$), 6.99–8.5 (m, 7H, Ar-H), 10.28 (s, 1H, −NH, D_2O exchangeable). ^{13}C-NMR (DMSO d_6/TMS): δ 13.4, 29.4, 47.5, 58.6, 76.4, 108.3, 109.2, 112.5, 114.5, 120.6, 122.8, 122.3, 127.6, 132.2, 135.7, 138.2, 144.2, 150.5, 158.7, 159.5, 167.2, 179.3; m/z (M^++1): 452. *Anal.* Calcd for $C_{23}H_{18}ClN_3O_5$ (451.31): C, 61.14; H, 4.02; N, 9.30; Cl, 7.85% Found: C, 61.19; H, 4.05; N, 9.34; Cl, 7.88%.

4i (R = Br, X = $COOC_2H_5$): ethyl 2′-amino-5-bromo-6′-methyl-2,5′-dioxo-5′,6’dihydrospiro [indoline-3,4′-pyrano[3,2-c]quinoline]-3′-carboxylate. Yield: 86%; Time: 8 min;

MP: 284–86°C; IR (KBr): 3379, 3258 (unequal doublet, asymmetric, and symmetric stretchings of −NH2), 2220 (sharp, medium, −CN), 1701, 1660, 1631 cm^{-1} (−CO-group, broad); ^{1}H-NMR (DMSO d_6/TMS): δ 0.93 (t, 3H, CH_3) 3.7 (s, 3H, $-NCH_3$), 4.35 (q, 2H, $-CH_2$), 6.6 (s, 2H, $-NH_2$), 6.94–8.8 (m, 7H, Ar-H), 10.48 (s, 1H, −NH, D_2O exchangeable). ^{13}C-NMR (DMSO d_6/TMS): δ 13.5, 29.3, 47.7, 58.4, 76.7, 108.2, 109.6, 112.1, 114.3, 120.7, 122.2, 122.1, 127.3, 132.0, 135.2, 138.8, 144.6, 150.3, 158.1, 159.9, 167.3, 179.5; m/z (M^++1): 496. *Anal.* Calcd for $C_{23}H_{18}BrN_3O_5$ (495.13): C, 55.66; H, 3.66; N, 8.47; Br, 16.10% Found: C, 55.69; H, 3.62; N, 8.43; Br, 16.15%.

4j (R = I, X = $COOC_2H_5$): ethyl-2′-amino-5-iodo-6′-methyl-2,5′-dioxo-5′,6'dihydrospiro[indoline-3,4′-pyrano[3,2-c]quinoline]-3′-carboxylate. Yield: 90%; Time: 6 min; MP: 220–22°C; IR (KBr): 3389, 3268 (unequal doublet, asymmetric, and symmetric stretchings of $-NH_2$), 2202 (sharp, medium, −CN), 1700, 1665, 1635 cm^{-1} (−CO-group, broad); ^{1}H-NMR (DMSO d_6/TMS): δ 0.96 (t, 3H, CH_3) 3.4 (s, 3H-NCH_3), 4.55 (q, 2H, $-CH_2$) 6.7 (s, 2H, $-NH_2$),6.73–8.6 (m, 7H, Ar-H), 10.36 (s, 1H, −NH, D_2O exchangeable). ^{13}C-NMR (DMSO d_6/TMS): δ 13.6, 29.1, 47.8, 58.3, 76.8, 108.3, 109.9, 112.4, 114.7, 120.9, 122.3, 122.3, 127.7, 132.8, 135.7, 138.7, 144.5, 150.1, 158.6, 159.3, 167.8, 179.6; m/z (M^++1): 544. *Anal.* Calcd for $C_{23}H_{18}IN_3O_5$ (543.01): C, 50.84; H, 3.34; N, 7.73; I, 23.36% Found: C, 50.88; H, 3.39; N, 7.77; I, 23.32%.

CONCLUSION

We have developed green and efficient method for the three-component synthesis of spirooxindoles **4(a–j)** by using DBU Acetate is convenient reaction medium. The main advantages of this reaction is provides high yields, easy workup, and inexpensive catalyst. All the synthesized compounds were evaluated for their biological activity, compounds **4b, 4e, 4f, 4g, 4j** exhibited moderate activity against all the tested strains with standard gentamicin.

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