One-Pot, Four-Component Synthesis of Novel Spiro[indeno[2,1-*b*]quinoxaline-11,4′-pyran]-2′-amines

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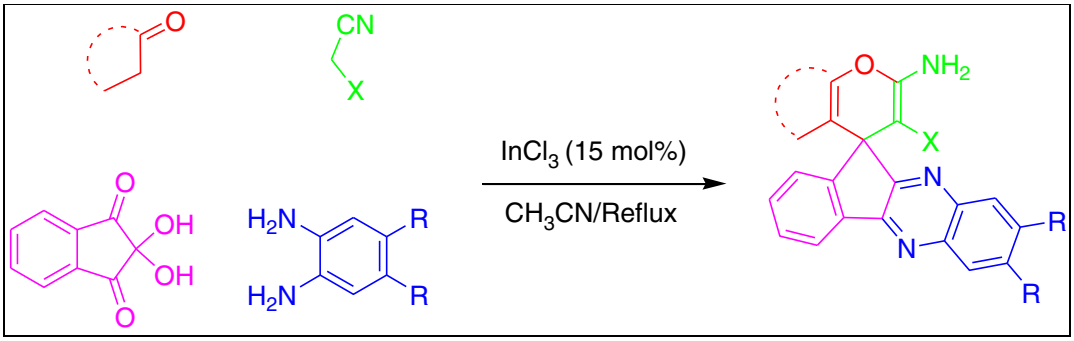

A one-pot, four-component reaction for the efficient synthesis of novel spiro[indeno[2,1-*b*]quinoxaline-11,4′-pyran]-2′-amines by using $InCl_3$ is described. The syntheses are achieved by reacting ninhydrin with 1,2-diaminobenzenes to give indenoquinoxalines, which are trapped *in situ* by alkyl malonates and various α-methylencarbonyl compounds through cyclization, providing multifunctionalized spiro-substituted indeno [2,1-*b*]quinoxaline-11,4′-pyran-2′-amines.

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INTRODUCTION

Functionalized nitrogen-containing and oxygen-containing heterocycles play a predominant role in medicinal chemistry, and they have been intensively used as scaffolds for drug development [1]. Multicomponent reactions have emerged as a powerful tool for delivering the molecular diversity needed in the combinatorial approaches for the preparation of bioactive compounds [2].

4*H*-Pyran pharmacophore is an important kernel structure of many natural products [3]. It plays an important role in the field of medicinal chemistry because of the various potential biological and pharmacological activities of its derivatives [4], such as inhibiting tyrosinase [5] and acting as anti-influenza virus agents [6]. Furthermore, these derivatives can be employed as pigments [7], fluorescent reagents [8], and photoactive materials [9]. Moreover, indenoquinoxalines exhibit diverse functions such as anti-metabolism and antitubercular properties [10]. Recently, quinoxaline derivatives have been found with good *in vitro* selectivity against *M. tuberculosis* (Fig. 1) [11]. The spirooxindole system is the core structure of many pharmacological agents and natural alkaloids [12–16]. For example, cytostatic alkaloids as spirotryprostatins A, B, and pterpodine have been shown to modulate the function of muscarinic serotonin receptors [17]. Condensed heterocyclic compounds containing a 2-oxindole nucleus or a 4*H*-pyrano fragment have different pharmacological activities, for example, spirocyclic 2-oxindole systems form the basis of such alkaloids as alstonisine and macroxin from the plants of the *Alstonia* genus [18,19] (Fig. 1).

The development of catalytic organic synthesis using air-stable and water-tolerant inorganic salts as Lewis acid catalyst is one of the important and challenging subjects in organic synthesis chemistry [20]. In recent years, indium (III) chloride has received considerable attention as an inexpensive, nontoxic, readily available catalyst for various transformations under mild and convenient conditions, affording the corresponding products in excellent yields with high selectivity [21].

Recently, Shanthi et al. [22] have utilized $InCl_3$ as an efficient catalyst for the three-component condensation reaction of malononitrile and 1-phenyl-3-methyl pyrazolon-5-one and carbonyl compounds for the synthesis of benzo[*b*]pyran derivatives. In continuation of our recent studies on green protocols, multicomponent reactions, synthesis of quinoxalines, and spiro compounds [23], herein, we report a one-pot, four-component method for the synthesis of novel spiro[indeno[2,1-*b*]quinoxaline-11,4′-pyran]-2′-amines from ninhydrin (**1**), 1,2-diaminobenzenes (**2a**, **b**), alkylmalonates (**3a–c**) and α-methylencarbonyl compounds (**4a–e**) in the presence of Indium (III) chloride as a nontoxic and effective inorganic catalyst (Scheme 1).

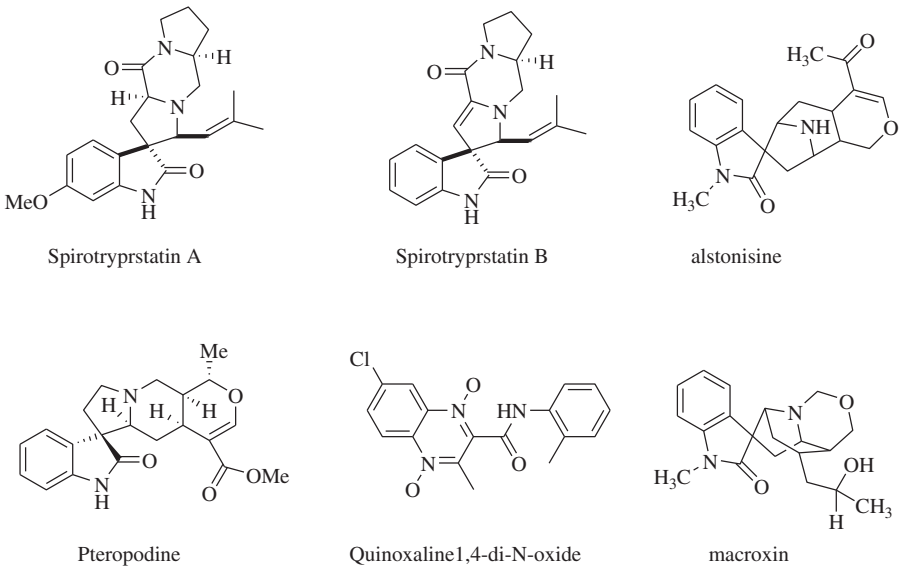
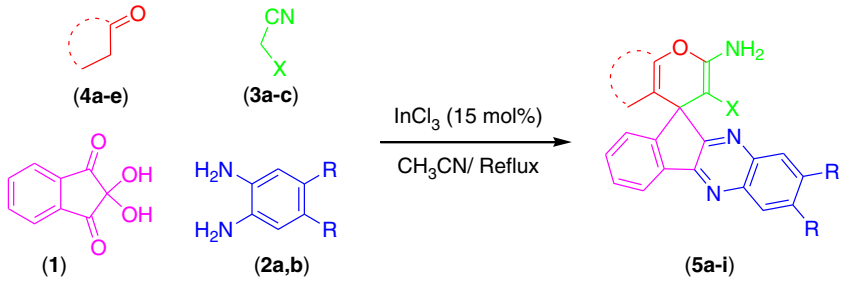


Figure 1. Representative structure of biologically active spiroxindole and quinoxaline derivatives.

Scheme 1. One-pot, four-component synthesis of spiro[indeno[2,1-*b*]quinoxaline-11,4′-pyran]-2′-amine derivatives in the presence of $InCl_3$.



RESULTS AND DISCUSSION

To establish the optimum conditions for the synthesis of the titled compounds, initially, the influence of the reaction temperature, the amounts of catalyst, and the reaction time were tested in different solvents and optimized. For this propose, a reaction between ninhydrin (**1**) (1 mmol), 1,2-diamino benzene (**2a**) (1 mmol), malononitrile (**3a**) (1 mmol), and 3,3-dimethyl 1,3 cyclohexanedione (**4a**) were examined as the model reaction in the presence of indium (III) chloride to form the product **5a** (Scheme 1 and Table 1).

After a complete screen search, we found that the maximum reaction rate as well as yield was obtained in the presence of 15 mol% of $InCl_3$ in acetonitrile at reflux conditions. Increasing the amount of catalyst to more than 20 mol% showed no substantial improvement in the yield, whereas the yield decreased when the amount of the catalyst was 10 mol%. At room temperature, the reaction was found to be very slow, and it was increased in higher temperatures, and at reflux conditions, the reaction rate was found to be a maximum. During our optimization studies, various solvents were examined, and CH_3CN was the best solvent. Moreover, it was observed that the reaction did not proceed efficiently in the absence of $InCl_3$ even after 48 h.

To test the generality and functional group tolerance of this procedure in the direct synthesis of spiro-substituted indeno[2,1-*b*]quinoxaline-11,4′-pyran-2′-amines, various alkylmalonates and α-methylencarbonyl compounds were condensed with ninhydrin and 1,2-diaminobenzenes in the presence of $InCl_3$ as catalyst (15 mol%) under the optimized conditions to afford the corresponding products, and obtained results were summarized in Table 2.

As Table 2 indicates, more active alkylmalonate (malononitrile **3a**) as well as less active alkylmalonates (methyl cyanoacetate **3b** and ethyl cyanoacetae **3c**) was applied successfully to afford the corresponding spiro [indeno[2,1-*b*]quinoxaline-11,4′-pyran]-2′-amines in excellent yields. This method tolerated key functional groups of five types of α-methylene carbonyl compounds. Moreover,

Table 1

One-pot, four-component synthesis of compound **5a** in the presence of $InCl_3$ as catalyst at various conditions.

Entry	Catalyst (mol%)	Reaction conditions	Time (h)	Yield (%)[a]
1	10	CH_3CN, reflux	15	78
2	15	CH_3CN, reflux	11	91
3	20	CH_3CN, reflux	12	90
4	15	CH_3CN, room temperature		
5	15	EtOH, reflux	12	73
6	15	$CHCl_3$, reflux	24	40
7	15	EtOAc, reflux	24	54
8	15	H_2O, reflux	24	Trace
9	—	CH_3CN, reflux	48	Trace

[a]Isolated yields.

two types of 1,2 diamino benzenes were used as starting materials. As can be seen in Table 2, the efficiency of the reaction did not changed in the presence of either 1,2 diamino benzene or 3,4 dimethyl 1,2 diamino benzene. With the proposed mechanism, the facilitation in the indenoquinoxaline (**A**) formation step, the substitution on the diamino benzene did not effect on the reaction rate. Our proposed mechanism for the synthesis of spiro[indeno[2,1-*b*]quinoxaline-11,4′-pyran]-2′-amine compounds **5** in the presence of $InCl_3$ is shown in Scheme 2. We envisioned that this reaction could be realized in a one-pot, two-step manner. Initially, ninhydrin **1** and the 1,2-phenylenediamine **2** reacted to form the corresponding indenoquinoxaline **A** in the presence of indium (III) chloride. Knovenagel condensation of the indenoquinoxaline **A** with alkyl malonate derivatives **3** affords an intermediate **B**, which undergoes Michael addition with the enolate form of carbonyl compound **4**. The enolate oxygen of this intermediate **C** attacks the nitrile group, and subsequent proton shift leads to compounds **5**.

CONCLUSION

In conclusion, we have developed a clean, simple, one-pot, four-component method for the synthesis of new spiroindenoquinoxaline derivatives catalyzed by indium (III) chloride in acetonitrile under reflux conditions. This method is bestowed with several unique merits, such as high conversions, simplicity in operation, multicomponent synthesis, and cost efficiency and thus significantly contributes to the practice of green chemistry. The biological evaluations of these derivatives are underway.

EXPRIMENTAL

All chemicals were commercially available and were purchased from Merck (Mumbai, India) or Fluka (New Delhi, India) chemical companies. The ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) were run on a Bruker Avance DPX-250, FT-NMR spectrometer. Microanalysis was performed on a Perkin-Elmer 240-B microanalyzer. Melting points were recorded on a Stuart Scientific Apparatus SMP3 (UK) in open capillary tubes.

General procedure for the synthesis of spiro[indeno [2,1-*b*]quinoxaline derivatives. Ninhydrin (1 mmol), 1,2-diaminobenzenes (1 mmol), and $InCl_3$ (15 mol%) were added in a 25-mL round-bottomed flask contained CH_3CN (15 mL) connected to a reflux condenser after about 10 min alkylmalonates (1 mmol), and α-methylencarbonyl compounds (1 mmol) were added to this mixture. The mixture was stirred at reflux conditions for the appropriate time (Table 1). Afterward, the reaction mixture was cooled to room temperature and was allowed to stand at 25°C for about 1 h. During this time, crystals of the product were formed and collected by filtration. To obtain the pure product, the product was washed with ethanol and diethyl ether (20 mL) two times and dried.

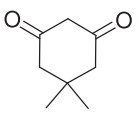
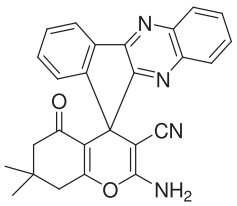
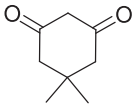
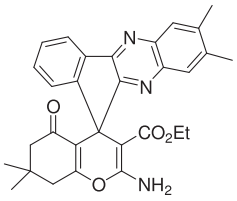
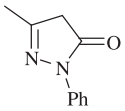
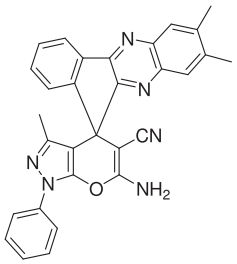
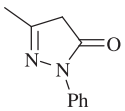
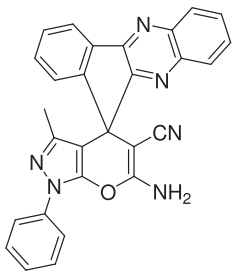
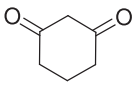
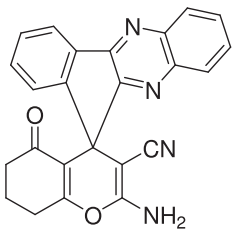
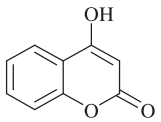
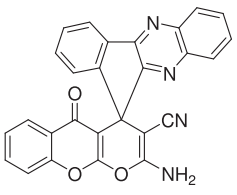
Selected spectral data ***2-Amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11′-indeno[2,1-b]quinoxaline]-3-carbonitrile (5a).*** White powder, mp = 280°C dec. υ_{max} (KBr) 3340, 3324, 3050, 2200, 1725, 1670, 1600, 1450 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): 1.00 (s, 3H), 1.03 (s, 3H), 1.97–2.08 (m, 2H), 2.61–2.75 (m, 2H), 7.33 (s, 2H), 7.51–7.55 (m, 2H), 7.59–7.60 (m, 1H), 7.75–7.78 (m, 1H), 7.81–7.84 (m, 1H), 8.05 (dd, J = 1.5, 8.2 Hz, 1H), 8.08 (d, J = 7.5 Hz, 1H), 8.15 (dd, J = 1.0, 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 27.5, 27.9, 31.9, 37.8, 43.8, 51.2, 56.3, 107.9, 114.8, 121.5, 124.6, 128.6, 129.0, 129.4, 129.5, 132.2, 138.6, 141.4, 141.7, 153.8, 157.3, 160.1, 164.2, 167.8, 169.4, 195.6. MS (*m/z*, %): 420 (M^+, 91.4); *Anal*. Calcd for $C_{26}H_{20}N_4O_2$: C, 74.27; H, 4.79; N, 13.33; found C, 74.31; H, 4.82; N, 13.36.

Ethyl 2-amino-7,7,7′,8′-tetramethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11′-indeno[2,1-b]quinoxaline]-3-carboxylate (5b). White powder, mp = 287°C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): 0.94 (s, 3H), 0.98 (s, 3H), 1.88 (d, J = 18.0 Hz, 1H), 2.42 (m, 3H), 2.46–2.53 (m, 6H), 2.60 (d, J = 18.5 Hz, 1H), 2.68 (d, J = 18.5 Hz, 1H), 3.20–3.21 (m, 2H), 7.35–7.46 (m, 3H), 7.69 (s, 1H), 7.87 (s, 1H), 7.95–7.97 (m, 3H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.7, 18.2, 19.4, 27.5, 28.7, 32.6, 47.9, 50.7, 51.1, 56.9, 59.2, 78.0, 109.0, 123.3, 126.1, 127.6, 127.7, 128.4, 128.9, 135.7, 137.6, 138.2, 141.1, 145.9, 146.2, 147.8, 152.9, 155.1, 161.6, 164.3, 199.1. *Anal*. Calcd for $C_{30}H_{29}N_3O_4$: C, 72.71; H, 5.90; N, 8.48; found C, 72.74; H, 5.88; N, 8.54.

6′-Amino-3′,7,8-trimethyl-1′-phenyl-1′H-spiro[indeno[2,1-b]quinoxaline-11,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5c). Pale yellow powder, mp = 248°C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): 1.09 (s, 3H), 2.42 (s, 3H), 2.47 (s, 3H), 7.36 (t, J = 7.2 Hz, 1H), 7.51 (t, J = 7.7 Hz, 2H), 7.63–7.64 (m, 5H), 7.85 (d, J = 9.0 Hz, 3H), 7.97 (s, 1H), 8.14 (t, J = 3.7 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.6,

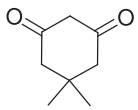
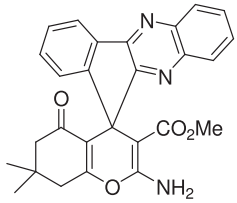
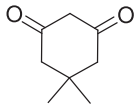
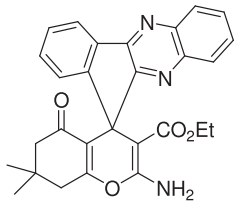
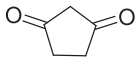
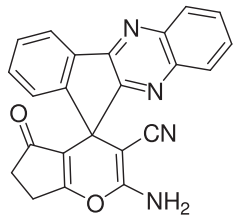
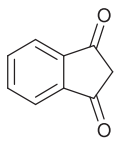
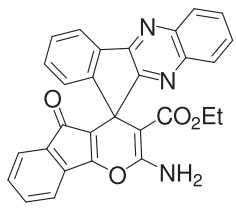
Table 2

One-pot four-component synthesis of spiro[indeno[2,1-*b*]quinoxaline-11,4′-pyran]-2′-amine derivatives.

Entry	R	X	Carbonyl compound	Product	Time (h)	Yield (%)[a]
5a	H	CN			11	91
5b	CH_3	CO_2Et			14	91
5c	CH_3	CN			11	90
5d	H	CN			10	93
5e	H	CN			13	91
5f	H	CN			14	93

(*Continues*)

Table 2
(Continued)

Entry	R	X	Carbonyl compound	Product	Time (h)	Yield (%)[a]
5g	H	CO_2Me			14	91
5h	H	CO_2Et			14	92
5i	H	CN			13	91
5j	H	CO_2Et			13	90

[a]Isolated yields.

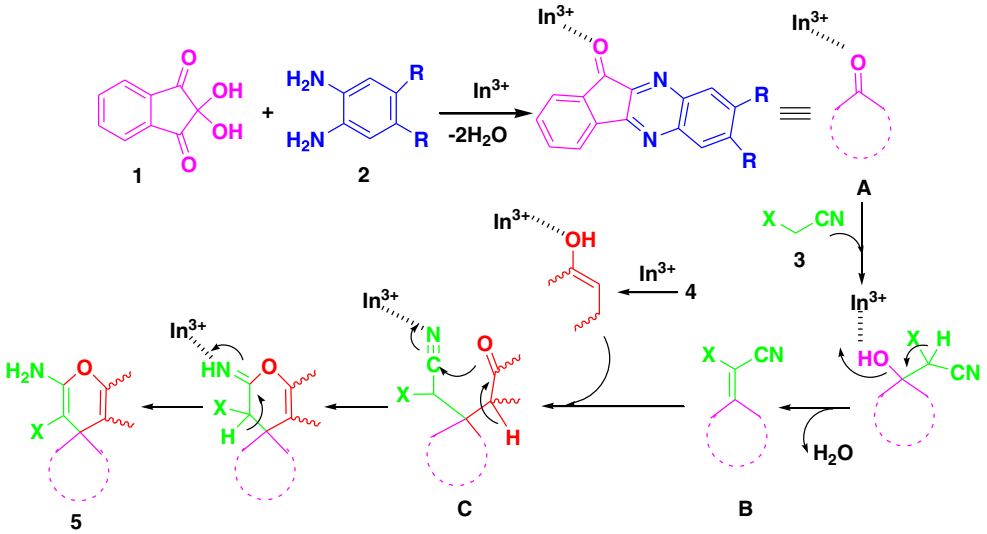
20.5, 20.6, 48.6, 58.7, 98.3, 118.9, 120.9, 122.2, 126.8, 127.4, 128.9, 129.1, 130.3, 130.5, 133.3, 136.9, 138.2, 140.8, 141.0, 141.5, 141.8, 144.6, 146.0, 150.9, 152.8, 161.9, 163.4. *Anal*. Calcd for $C_{30}H_{22}N_6O$: C, 74.67; H, 4.60; N, 17.42; found C, 74.62; H, 4.63; N, 17.48.

6-Amino-3′-methyl-1′-phenyl-1′H-spiro[indeno[2,1-b]quinoxaline-11,4′-pyrano[2,3-c]pyrazole]-5′-carbonitrile (5d). Pale yellow powder,(mp = 240°C [dec.], 236°C [19]). ^{1}H NMR (DMSO-d_6, 500 MHz): 1.10 (s, 3H), 7.37 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.7 Hz, 2H), 7.64–7.71 (m, 5H), 7.81–7.90 (m, 4H), 8.12 (d, J = 8.5 Hz, 1H), 8.20 (t, J = 8.5 Hz, 2H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 12.6, 48.6, 58.7, 116.9, 118.9, 121.8, 122.7, 125.8, 125.9, 128.8, 128.91, 128.97, 129.0, 129.6, 129.8, 129.9, 135.9, 136.7, 136.9, 139.8, 142.3, 146.1, 154.2, 159.1, 175.9. *Anal*. Calcd for $C_{28}H_{18}N_6O$: C, 74.00; H, 3.99; N, 18.49; found C, 74.10; H, 4.09; N, 18.56.

2-Amino-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11′-indeno[2,1-b]quinoxaline]-3-carbonitrile (5e). White powder, mp = 278°C dec. υ_{max} (KBr) 3370, 3342, 3160, 2200, 1680, 1662, 1600, 1345 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): 1.89–1.94 (m, 2H), 2.07–2.14 (m, 2H), 2.73–2.81 (m, 2H), 7.33 (s, 2H), 7.52–7.61 (m, 2H), 7.75–7.84 (m, 2H), 8.06–8.09 (m, 2H), 8.16 (dd, J = 1.0, 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 20.6, 27.8, 37.4, 48.0, 59.5, 113.8, 118.4, 122.2, 125.5, 129.66, 129.69, 129.7, 129.9, 130.5, 136.9, 141.7, 142.4, 152.9, 155.0, 159.6, 166.5, 167.5, 195.9. *Anal*. Calcd for $C_{24}H_{16}N_4O_2$: C, 73.46; H, 4.11; N, 14.28; found C, 73.54; H, 4.18; N, 14.36.

2′-Amino-5′-oxo-5′H-spiro[indeno[2,1-b]quinoxaline-11,4′-pyrano[2,3-b]chromene]-3′-carbonitrile (5f). White powder, mp = 297°C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): 7.44 (d, J = 8.0 Hz, 1H), 7.57–7.63 (m, 3H), 7.74–7.81 (m, 5H), 7.84–7.86 (m, 1H), 8.05–8.08 (m, 2H), 8.15–8.20 (m, 1 H), 8.19–8.21 (dd, J = 1.0, 8.5 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 113.5, 117.5, 118.0, 122.5, 123.7, 125.9, 126.3, 129.81, 129.88, 130.3, 130.4, 131.0,

Scheme 2. The proposed mechanism for the synthesis of spiro[indeno[2,1-b]quinoxaline-11,4′-pyran]-2′-amine derivatives **5** in the presence of $InCl_3$.



133.4, 134.5 137.3, 141.8, 142.8, 151.5, 153.0, 154.8, 156.5, 159.1, 159.4, 165.4. *Anal*. Calcd for $C_{27}H_{14}N_4O_3$: C, 73.30; H, 3.19; N, 12.66; found C, 73.36; H, 3.25; N, 12.69.

Methyl 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro [chromene-4,11′-indeno[2,1-b]quinoxaline]-3-carboxylate (5g). White powder, mp = 269°C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): 0.94 (s, 3H), 0.99 (s, 3H), 1.84–2.01 (m, 2H), 2.56–2.74 (m, 2H), 2.82 (s, 3H), 7.38–7.48 (m, 3H), 7.64–7.74 (m, 2H), 7.88 (s, 2H), 7.92–7.93 (m, 1H), 8.02 (d, J = 7.0 Hz, 1H), 8.09–8.11 (m, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 19.4, 27.5, 28.7, 32.6, 47.9, 50.7, 51.2, 78.0, 114.8, 121.6, 124.6, 128.6, 129.0, 129.45, ? >129.49, 132.2, 138.6, 141.4, 141.7, 153.8, 157.3, 160.1, 164.2, 167.8, 169.4, 195.7. *Anal*. Calcd for $C_{27}H_{23}N_3O_4$: C, 71.51; H, 5.11; N, 9.27; found C, 71.54; H, 5.19; N, 9.36.

Ethyl 2-amino-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydrospiro[chromene-4,11′-indeno[2,1-b]quinoxaline]-3-carboxylate (5h). White powder, mp = 272°C dec. ^{1}H NMR (DMSO-d_6, 500 MHz): 0.99 (s, 3H), 1.04 (s, 3H), 1.08 (t, J = 7.0 Hz, 3H), 1.85–2.01 (m, 2H), 2.56–2.74 (m, 2H), 3.32–3.45 (m, 2H), 7.39 (d, J = 7.5 Hz, 1H), 7.44 (t, J = 7.2 Hz, 1H), 7.49 (t, J = 7.2, 1H), 7.65–7.68 (m, 1H), 7.71–7.74 (m, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.98 (s, 2H), 8.02 (d, J = 7.0 Hz, 1H), 8.10 (d, J = 8.5 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 13.7, 19.4, 27.5, 28.7, 32.5, 47.8, 51.3, 56.8, 59.2, 77.8, 114.9, 121.5, 124.7, 128.6, 129.0, 129.4, 132.2, 138.8, 141.3, 141.8, 153.9, 157.5, 160,4, 164.2, 167.9, 169.4, 195.7. *Anal*. Calcd for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99; found C, 71.99; H, 5.42; N, 9.05.

2-Amino-7′,8′-dimethyl-5-oxo-6,7-dihydro-5H-spiro[cyclopenta [b]pyran-4,11′-indeno[2,1-b]quinoxaline]-3-carbonitrile (5i). White powder, mp = 274°C dec. υ_{max} (KBr) 3350, 3334, 3120, 2190, 1676, 1662, 1595, 1340 cm^{-1}. ^{1}H NMR (DMSO-d_6, 500 MHz): 2.31–2.32 (m, 2H), 2.90–2.91 (m, 2H), 7.59–7.65 (m, 5H), 7.79–7.82 (m, 1H), 7.85–7.88 (m, 1H), 8.11–8.13 (m, 2H), 8.19 (d, J = 8.0 Hz, 1H). ^{13}C NMR (DMSO-d_6, 125 MHz): δ 25.8, 34.1, 47.5, 58.4, 116.9, 118.5, 122.4, 126.3, 129.8, 129.9, 130.3, 131.1, 133.4, 137.0, 141.9, 142.8, 150.8, 154.5, 161.7, 164.1, 178.8, 200.7. *Anal*. Calcd for $C_{25}H_{18}N_4O_2$: C, 73.88; H, 4.46; N, 13.78; found C, 73.93; H, 4.40; N, 13.81.]

Ethyl 2-amino-5-oxo-5H-spiro[indeno[1,2-b]pyran-4,11′-ineno [2,1-b]quinoxaline]-3-carboxylate (5j). White powder, mp = 289°C dec. ^{1}H NMR ($CDCl_3$, 500 MHz): 2.04 (t, J = 12.25 Hz, 3H), 5.22 (m, 2H), 7.26–7.29 (m, 1H), 7.37–7.42 (m, 2H), 7.43–7.45 (m, 1H), 7.53 (t, J = 8.5 Hz, 2H), 7.57–7.59 (m, 2H), 7.62–7.65 (m, 3H), 7.66–7.73 (m, 1H), 8.03 (d, J = 4.0 Hz, 1H), 8.12 (d, J = 3.77 Hz, 1H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ 31.3, 52.5, 123.4, 124.3, 129.1, 129.3, 129.4, 129.7, 129.9, 132.1, 135.9, 136.2, 138.3, 141.1, 142.3, 142.4, 146.0, 154.1, 160.8. *Anal*. Calcd for $C_{29}H_{19}N_3O_4$: C, 73.56; H, 4.04; N, 8.87; found C, 73.29; H, 4.12; N, 9.05.

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