CHAPTER 5

ONE-POT FOUR-COMPONENT SYNTHESIS OF SPIRO[INDOLINE-3,4'-QUINOLINE] DERIVATIVE USING DABCO AS A GREEN CATALYST

One-pot four-component synthesis of spiro[indoline-3,4'-quinoline] derivative using DABCO as a green catalyst

5.1 Introduction

The philosopher's stone is catalysis in chemical industries, which acts as a driving force for chemical reactions [1, 2]. Catalysts play an important role in forming an extensive range of value-added products crucial to humans. A coherent and scientific design of proficient catalysts is vital to improving the performance of chemical reactions. The synthetic procedures can be planned in a more powerful, ecological, and cheap fashion through the attentive use of catalysts. There are two types of catalysts, i. e. homogenous and heterogeneous, based on the nature of catalysts and reactants. A homogenous catalyst retains a similar phase with the reactants as a heterogeneous catalyst [3, 4]. Homogeneous catalysis is becoming more critical to industrial and organic chemists [5] and offers benefits like improved selectivity, increased activity, and avoiding mass transfer limitations, which may permit lower temperatures [6].

Diazabicyclo [2.2.2] octane (DABCO) is a weak base and ligand and is used as a catalyst in several chemical reactions [7]. It is a cage-like small diazabicyclic molecule that has medium hindrance. Alternatively, it is also utilized in several reactions, such as the Baylis-Hillman reaction [8], N- methylation of indoles, Lu's type cycloaddition umpolung addition, etc. [9]. Organic chemists are more attracted to using DABCO as a catalyst because it is cheap, commercially available, safe, and non-toxic [10].

A moment ago, heterocyclic compounds containing Quinolone moiety had attracted much more attention of organic chemists due to its various industrial application[11], for example, in agrochemical [12], medicine [13], therapeutic agent [14], natural product [15], ligands in transition metal complexes [16], functional materials[17], organic light-emitting diodes[18], electrochemical storage devices [19], dyes [20], chemosensors [21], therapeutic agents, bioorganic, food colorants and pH indicators [22]. Additionally, quinolone derivatives are also significant biologically active compounds that show substantial biological activities like tuberculosis (TB) [23], antimicrobial [24], anti-HIV [25], anthelmintics [26], anti-inflammatories [27], antitumor [28], and antimalarial [29]. One of the most important quinolone derivatives, i.e., spiroindole, is found in many natural products and attracted the chemist's attention owing to its many biological activities [30] like antitubercular [31], antitumor [32], antimicrobial [33], antifungal [34], antimycobacterial [35], and antioxidant agents [36], etc. Isatin is the core unit of spiroindole molecule that shows many biological activities and is also utilized to synthesize several heterocyclic compounds, including spiroindole [37].

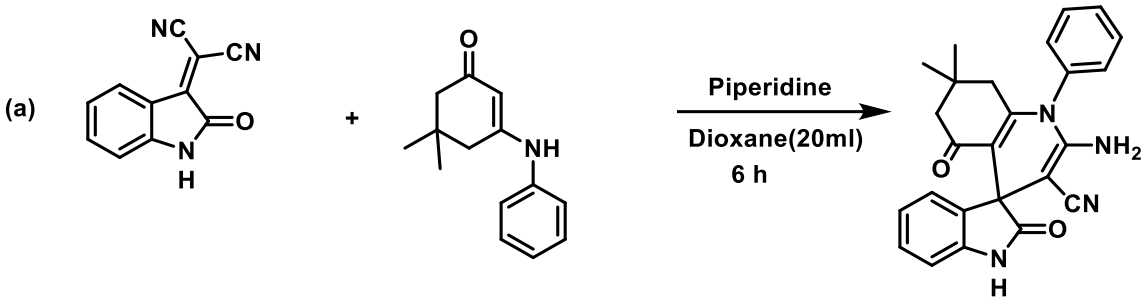
Multicomponent reactions are an essential tool for designing complex molecules in a single step to afford the target compounds, for example, spiroindole derivatives, etc., which combine most of the atoms of the starting materials [38] without intermediate isolation. MCRs are more potent than the conventional multi-step method because of their energy efficiency, better atom economy, simple operation, and excellent yield [39]. This approach

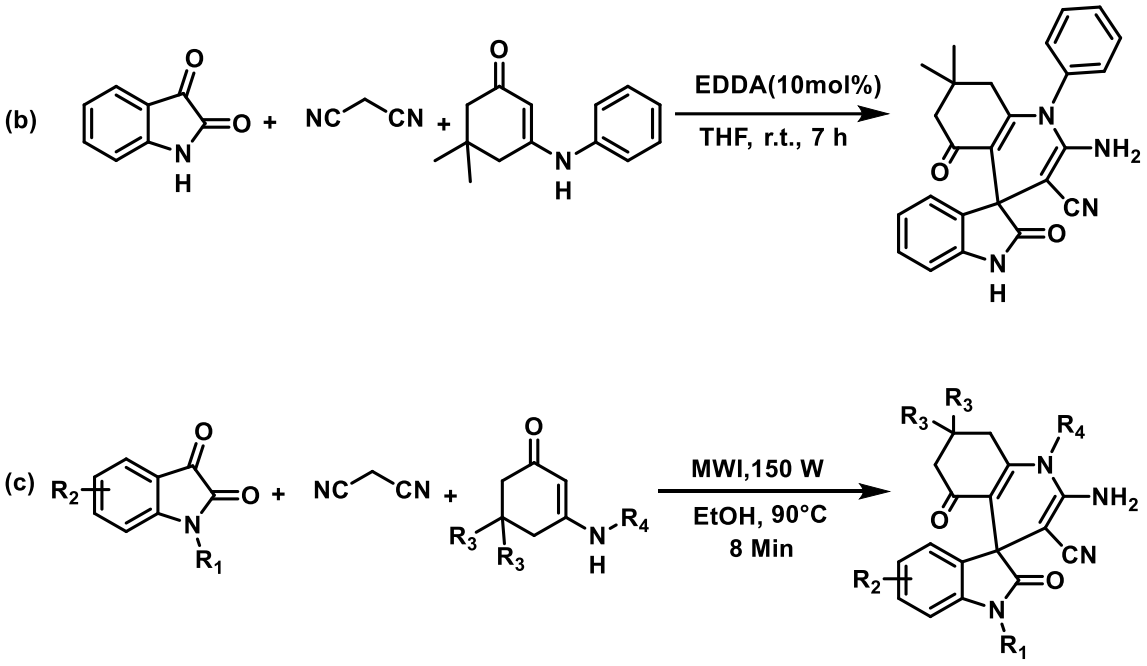
is environmentally friendly, time-saving, and has more straightforward and affordable purification procedures [40].

Due to the importance of spiro [Indoline-3, 4'-Quinoline] derivatives, various synthetic approaches have been described [41-43]. However these methods are pretty helpful, but there are some drawbacks. Thus, there is space to design a new procedure that might work better than others. As far as we know, there is no report on the synthesis of spiroindole via a four-component reaction of amine, 1, 3-diketone, isatin, and active methylene compounds (malononitrile and ethyl acetoacetate) using non-toxic and cheap catalyst DABCO.

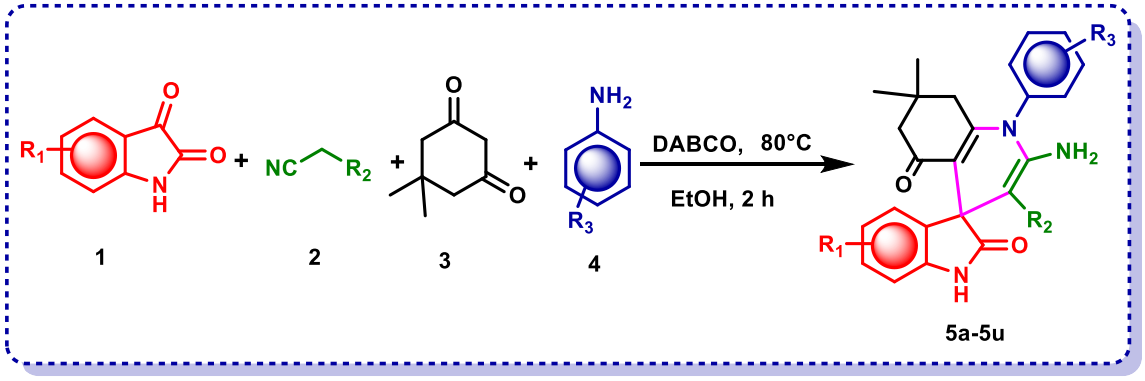
In light of the above and as a part of our research interest in developing the new synthetic approach [44], we have reported here the four-component reaction of amine, 1,3-diketone, isatin, and active methylene compounds (malononitrile and ethyl acetoacetate) to provide spiroindole using DABCO as a catalyst **(Scheme 5.1)**.

Previous Work:





This Work

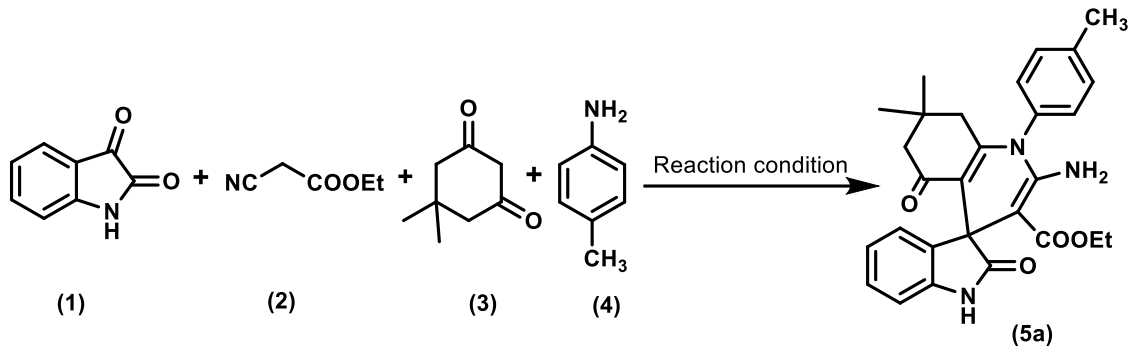


Scheme 5.1 Strategies for the synthesis of Spiro [Indoline-3, 4'-Quinoline]

5.2 Results and discussion

Mainly for optimization, a model reaction was chosen for carrying out a one-pot multicomponent reaction of amine (1mmol), dimedone (1mmol), isatin (1mmol), and malononitrile (1mmol) using DABCO in the presence of ethanol. Initially, the reaction was investigated using 10 mol% of different catalysts like Triethylamine, Piperidine, Imidazole, K_2CO_3, NaH, DBN and DBU, but they provided only 41, 62, 23, 65, 38, 52, and 56%, respectively (**Table 5.1, Entries 1-7**). Surprisingly 82% yield was obtained with 10 mol% of DABCO (**Table 5.1, Entry 8**). Now the amount of catalyst was examined, and it was found that 20 mol% of DABCO provided maximum yield, i.e., 95% yield of the product (**Table 5.1, Entry 10).** Various solvents like H_2O, THF, DMSO, DMF, Toluene, and CH_3CN were successfully examined, but none of them could provide the desired yield of the product. (**Table 5.1, Entries 13-18**). The reaction was also examined without catalyst (**Table 5.1, Entry 19**), without solvent (**Table 5.1, Entry 20**), and without both catalyst and solvent (**Table 5.1, Entry 21**). Only a trace amount of product was obtained without catalyst, while no product was formed in the last two cases (**Table 5.1, Entries 20, 21**). Finally, the temperature was also optimized, and it was found that 80^oC was the best for the reaction (**Table 5.1, Entries 22-24**).

Table 5.1 Optimization condition for the synthesis of Spiro [Indoline-3, 4'-Quinoline] **5a**[(a)]



Entry	Catalyst (Mol %)	Solvent	Temp.	Time(h)	Yield[(b)] (%)
1)	Triethylamine (10)	EtOH	80^0C	6	41
2)	Piperidine (10)	EtOH	80^0C	6	62
3)	Imidazole (10)	EtOH	80^0C	6	23
4)	K_2CO_3 (10)	EtOH	80^0C	6	65
5)	NaH (10)	EtOH	80^0C	6	38
6)	DBN (10)	EtOH	80^0C	2	52
7)	DBU (10)	EtOH	80^0C	2	56
8)	DABCO (10)	EtOH	80^0C	2	82
9)	DABCO (15)	EtOH	80^0C	2	88
10)	**DABCO (20)**	**EtOH**	**80^0C**	**2**	**95**
11)	DABCO (25)	EtOH	80^0C	2	90
12)	DABCO (5)	EtOH	80^0C	2	74
13)	DABCO (20)	H_2O	80^0C	2	32

14)	DABCO (20)	THF	80^0C	2	24
15)	DABCO (20)	DMSO	80^0C	2	15
16)	DABCO (20)	DMF	80^0C	2	13
17)	DABCO (20)	Toluene	80^0C	18	NA
18)	DABCO (20)	CH_3CN	80^0C	18	NA
19)	---------	EtOH	80^0C	24	Trace
20)	DABCO (20)	-----	80^0C	24	NA
21)	---------	-------	80^0C	24	NA
22)	DABCO (20)	EtOH	100^0C	2	85
23)	DABCO (20)	EtOH	120^0C	6	53
24)	DABCO (20)	EtOH	60^0C	6	40

[a]Experimental condition: Isatin(1 mmol), ethylcyanoacetate (1 mmol), dimedone (1 mmol), aniline (1 mmol), solvents (5 ml) , 80^0C, 2 hrs under DABCO (20 mol%) as a green catalyst

[b] isolated yields, [c] NA- no reaction

To find the effect of the molar proportion of the reaction mixture on the yield of the product and type of the product, a different molar proportion of the reactant was taken for the reaction (**Table 5.2**). The perusal of Table 5.2 indicates that there is no effect on the type of reaction at any proportion, and the best result was obtained when the molar proportion of all substrates (1, 2, 3, 4) was 1:1:1:1 (**Table 5.2, Entry 1)**.

Table 5.2 Effect of molar proportion of reaction mixture[(a)]

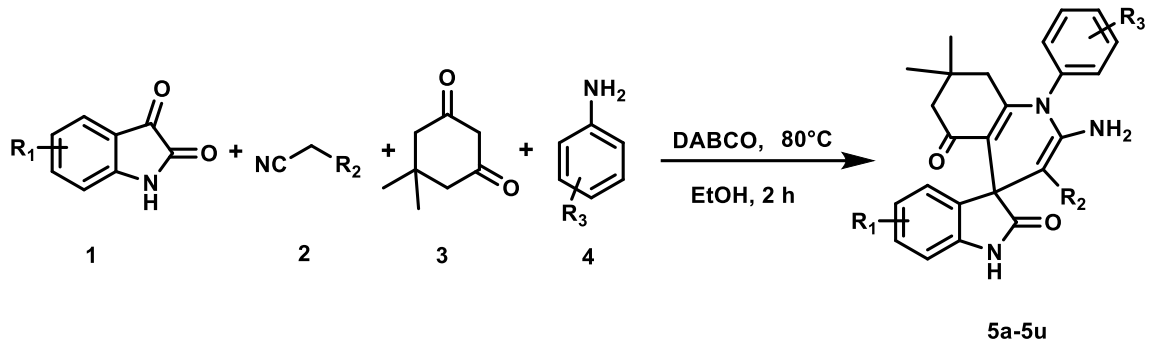
Isatin (mmol)	Ethyl cyanoacetate (mmol)	Dimedone (mmol)	Aniline (mmol)	Time (hrs)	Yield[b] (%)
1	1	1	1	24	95%
1	2	1	1	24	NA
2	1	1	1	24	NA
1	1	2	1	24	NA
1	1	1	2	24	NA

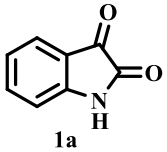
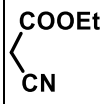
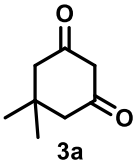
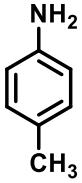
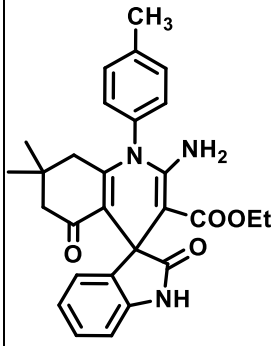
[a]Experimental condition: Isatin(1 mmol), ethylcyanoacetate (1 mmol), dimedone (1 mmol), aniline (1 mmol), solvents (5 ml) , 80^0C, 2 hrs under DABCO (20 mol%) as a green catalyst

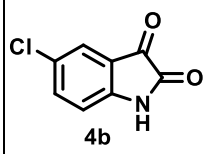
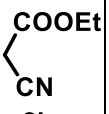
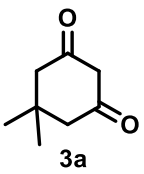
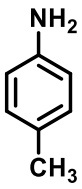
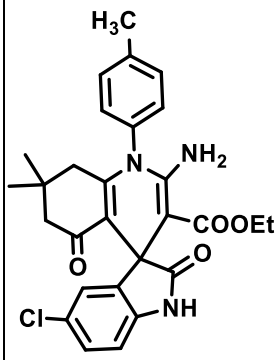
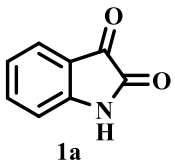
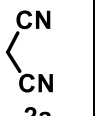
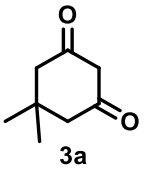
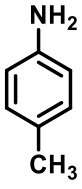
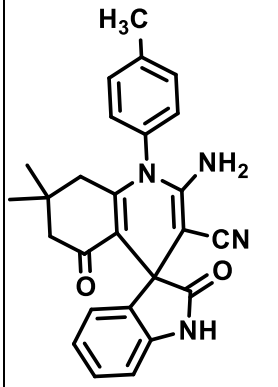
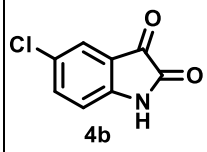
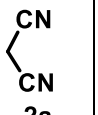
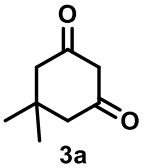
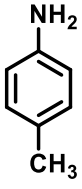
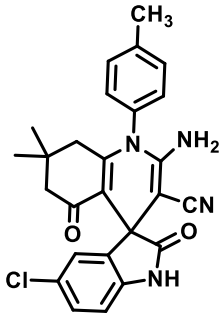
[b] isolated yields, [c] NA- no reaction

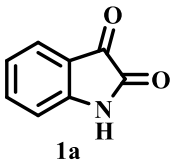
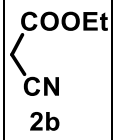
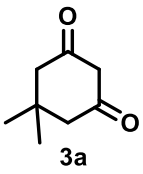
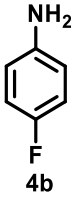
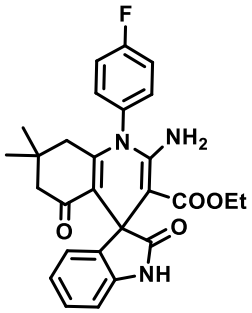
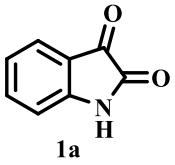
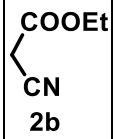
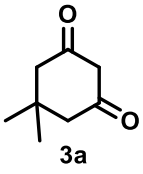
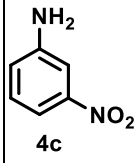
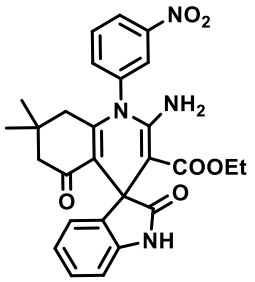
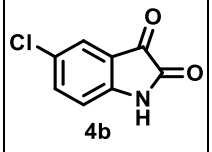
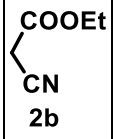
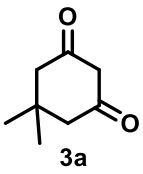
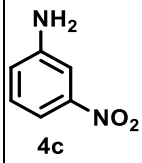
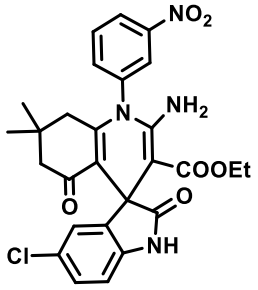
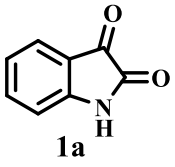
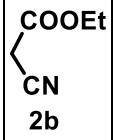
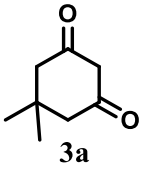
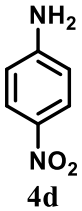
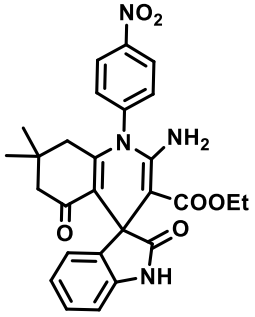
After optimizing reaction conditions, we explored the reaction's breadth and limitations in terms of isatin (**1a**), 5-bromoisatin **(1b)**, 5-chloroisatin **(1c),** and active methylene compounds like malononitrile **(2a)** and ethyl aceto- acetate **(2b)** react with dimedone **(3a)** and various amines like p-toluidine**(4a)**, 4-fluoroaniline**(4b)**, 3-nitroaniline**(4c)**, 4-nitroaniline**(4d)**, 3-chloroaniline**(4e)**, 4-(trifluoromethyl)aniline**(4f)**, 4-methoxyaniline**(4g)**. The reaction proceeds smoothly in all cases. However, when barbituric acid was substituted for malononitrile, the product's nature altered, and indoloindole was generated instead of spirocompounds (**Scheme 5.2**). Some more reactions were carried out to confirm the formation of indoloindole [41].

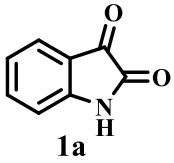
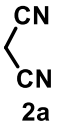
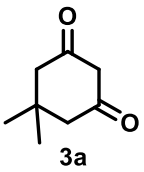
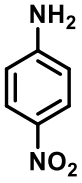
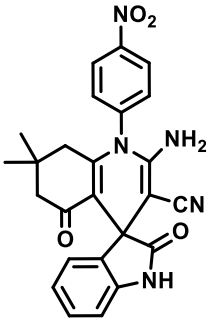
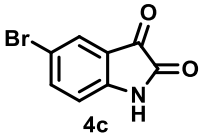
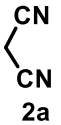
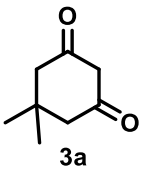
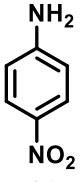
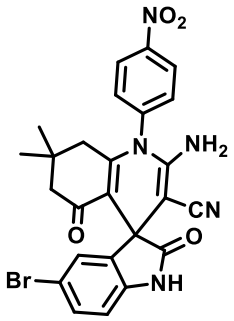
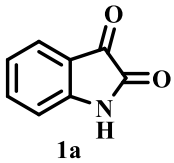
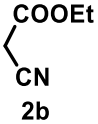
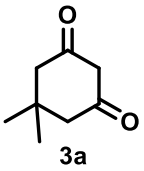
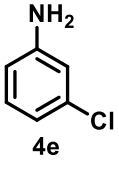
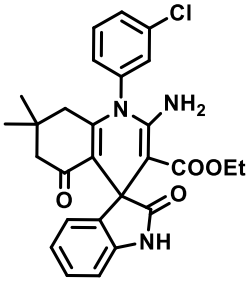
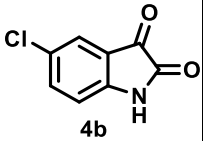
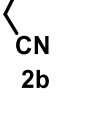
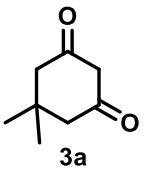
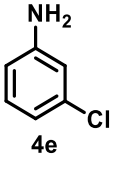
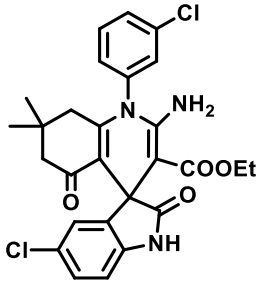
Table 5.3 Exploration of substrate scope for the synthesis of Spiro [Indoline-3, 4'-Quinoline][a]

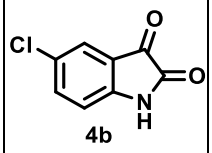
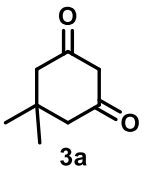
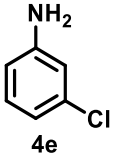
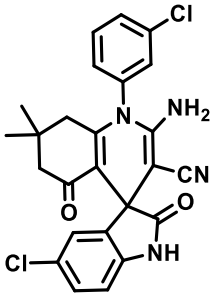
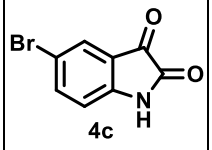
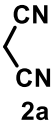
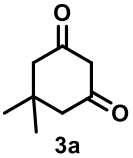
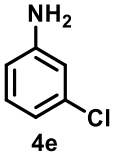
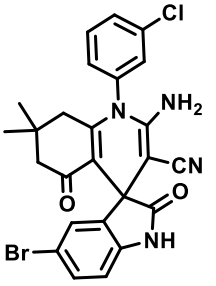
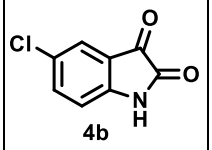
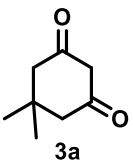
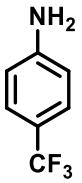
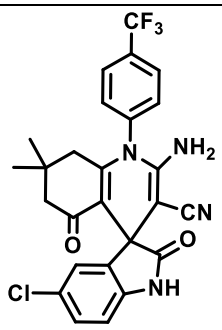
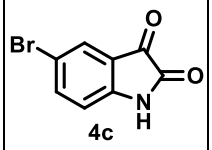
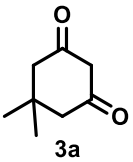
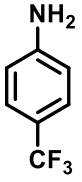
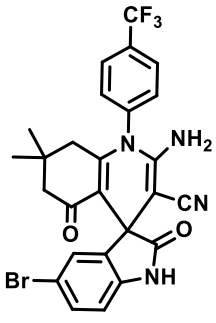


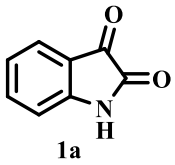
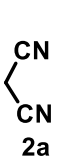
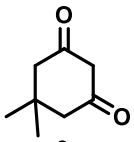
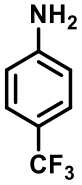
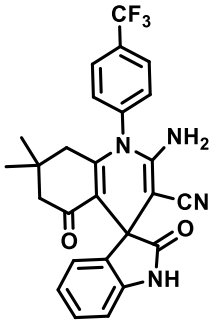
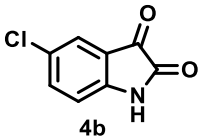
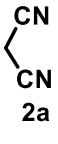
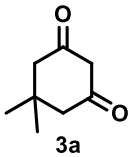
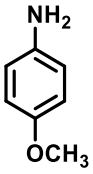
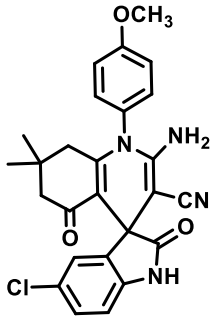
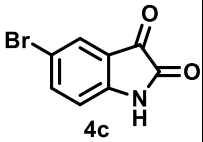
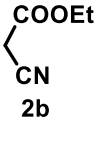
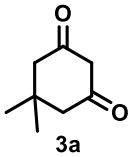
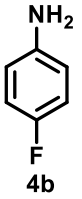
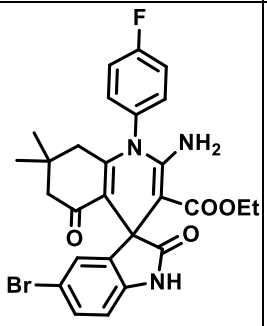
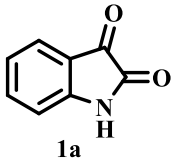
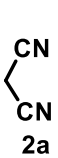
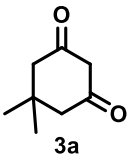
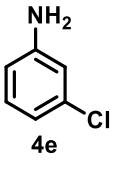
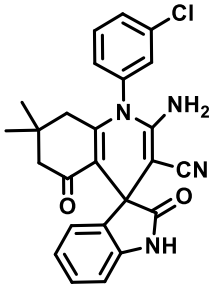
Entry	1	2	3	4	5[a]	Yield[b] (%)
4a	 1a	 2b	 3a	 4a		88

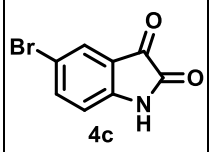
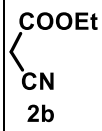
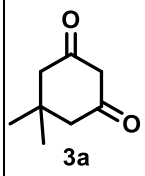
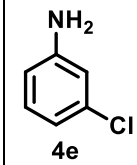
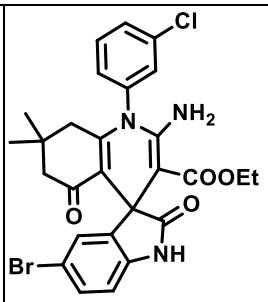
4b	 4b	 2b	 3a	 4a		**86**
4c	 1a	 2a	 3a	 4a		**88**
4d	 4b	 2a	 3a	 4a		**84**

4e	 **1a**	 **2b**	 **3a**	 **4b**		**82**
4f	 **1a**	 **2b**	 **3a**	 **4c**		**84**
4g	 **4b**	 **2b**	 **3a**	 **4c**		**80**
4h	 **1a**	 **2b**	 **3a**	 **4d**		**85**

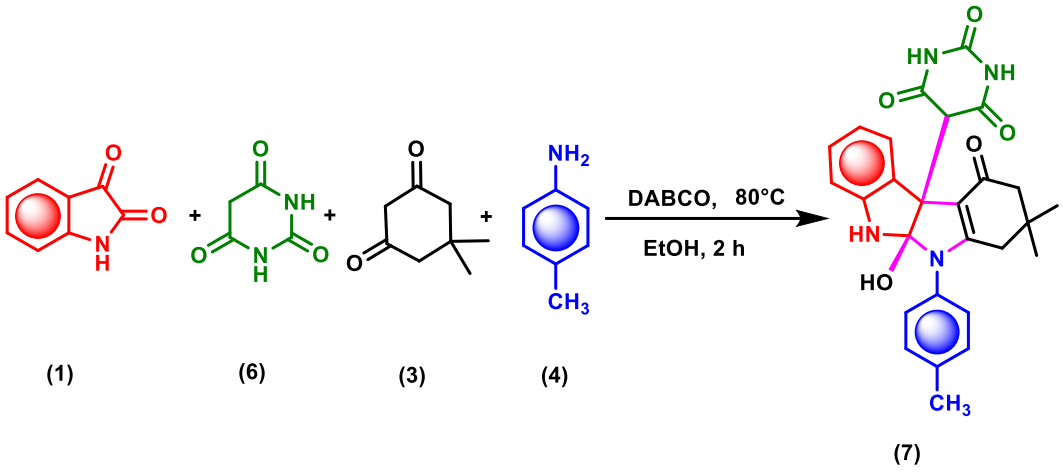
4i	 **1a**	 **2a**	 **3a**	 **4d**		**88**
4j	 **4c**	 **2a**	 **3a**	 **4d**		**86**
4k	 **1a**	 **2b**	 **3a**	 **4e**		**83**
4l	 **4b**	 **2b**	 **3a**	 **4e**		**82**

4m	 4b	 2a	 3a	 4e		**83**
4n	 4c	 2a	 3a	 4e		**85**
4o	 4b	 2a	 3a	 4f		**88**
4p	 4c	 2a	 3a	 4f		**88**

4q	 1a	 2a	 3a	 4f		**88**
4r	 4b	 2a	 3a	 4g		**87**
4s	 4c	 2b	 3a	 4b		**84**
4t	 1a	 2a	 3a	 4e		**86**

4u	 4c	 2b	 3a	 4e		**86**

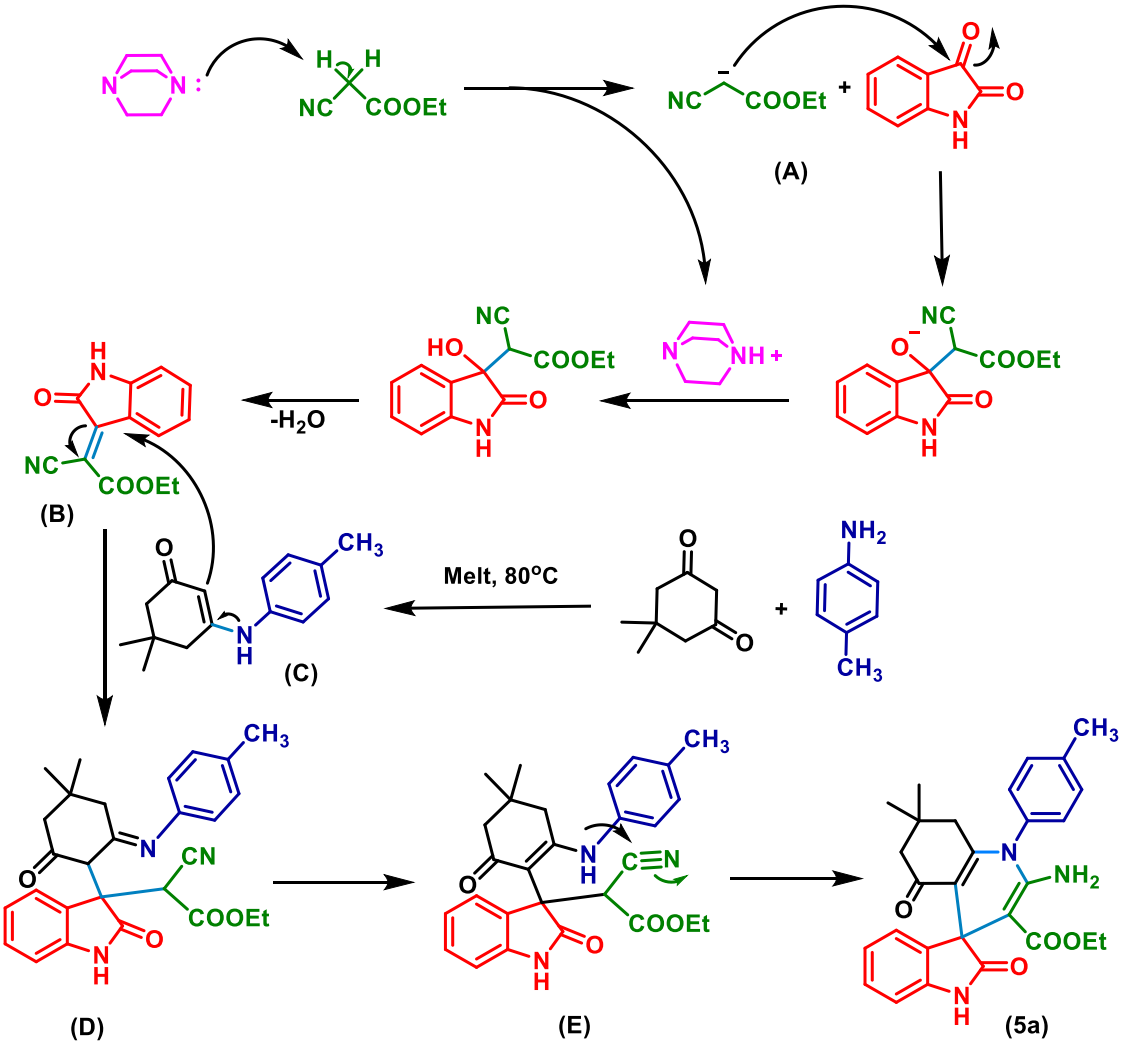
[a]Experimental condition: Isatin(1 mmol), ethylcyanoacetate (1 mmol), dimedone (1 mmol), aniline (1mmol), solvents (5ml) , 80^0C, 2 hrs, under DABCO (20mol%) as a green catalyst
[b]Isolated yields, [c] NA- no reaction



Scheme 5.2 Synthesis of Indoloindole pyrimidine derivatives

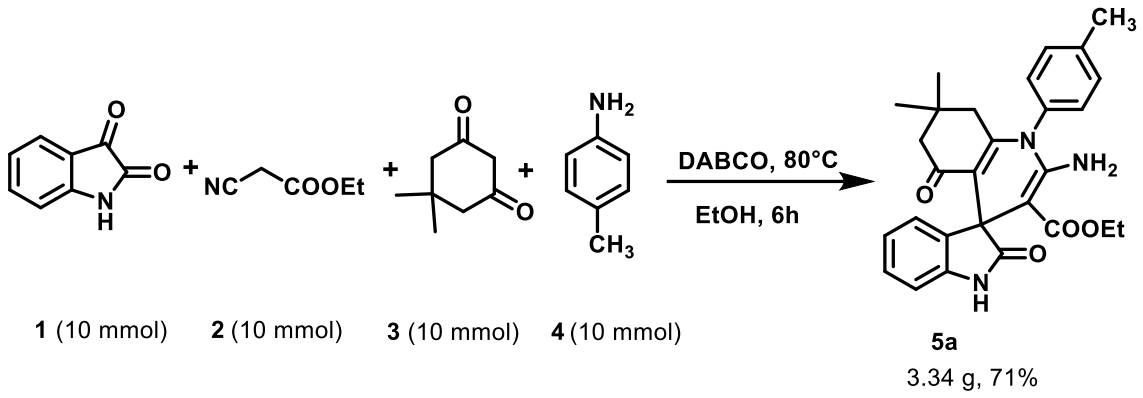
A probable mechanism (**Scheme 5.3**) of the reaction is projected based on product isolation in the presence of DABCO, represented in Scheme 5.3. Firstly, DABCO reacts with ethyl cyanoacetate, takes the acidic proton of the active methylene group, and gives the intermediate **A**. Then intermediate A reacts with isatin experienced Knoevenagel condensation in a solution to provide a cyanoolefin intermediate **B** with the elimination of water. The enaminone **C** (formed in situ from aniline and dimedone) reacts with intermediate

B through Micheal addition and provides **D**. Further, the intermediate **D** isomerizes to furnish **E**. The final product **5a** was formed by intramolecular cyclization (by the attack of nitrogen of **E** towards its cyano moieties).



Scheme 5.3 A plausible mechanism for the synthesis of Spiro [Indoline-3, 4'-Quinoline] **(5a)**

In addition, the practicality was confirmed by performing the model reaction on a gram scale (Figure 5). The mixture of isatin **1** (10 mmol), ethyl cyanoacetate **2** (10 mmol), dimedone **3** (10 mmol), aniline **4** (10 mmol), and DABCO catalyst was added to ethanol (50 ml) and stirred at 80°C for 6h. After completing the reaction (monitored by thin-layer chromatography), the solid product was obtained, which was filtered and washed with ethanol. The product was recrystallized with hot ethanol to give the desired product in good yield (**Scheme 5.4**).



Scheme 5.4 Synthesis of Spiro [Indoline-3, 4'-Quinoline] in gram scale.

5.3 Conclusion

In summary, we have established a simple, green, and efficient one-pot four-component strategy of isatin, ethyl cyanoacetate, dimedone, and aniline to synthesize spiro[Indoline-3,4'-quinoline] employing DABCO as a catalyst under ethanol as a solvent. The current approach produces good to excellent yields in a short reaction time. This approach works for gram-scale reactions as well.

5.4 Experimental section

5.4.1 General procedure for the synthesis of Spiro [Indoline-3, 4'-Quinoline] (5)

To the mixture of isatin **1** (1.0 mmol), ethyl cyanoacetate **2** (1.0 mmol), dimedone **3** (1.0 mmol) aniline **4** (1.0 mmol) and DABCO catalyst (20 mol %) was added to ethanol (5 ml) and stirred at 80°C for 2h. After completing the reaction (monitored by thin-layer chromatography), the solid product was obtained, which was filtered and washed with ethanol. The product was recrystallized with hot ethanol to give the desired product in good yield.

5.4.2 Analytical Data

Ethyl 2'-amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5a)

White solid, m.p. >300 °C, yield: 0.435 g, 93%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.09 (s, 1H), 7.44 (m, *J* = 8.4 Hz, 4H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.06 (m, *J* = 8.2 Hz, 1H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 3.79 – 3.64 (m, 2H), 2.43 (s, 3H), 2.06 (m, 2H), 1.86 (m, 2H), 0.84 (m, 6H), 0.77 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.19, 181.97, 169.00, 153.31, 151.48, 143.36, 140.48, 139.94, 133.78, 130.31, 129.42, 126.93, 124.59, 123.12, 112.46, 111.53, 109.24, 78.67, 58.98, 50.52, 49.68, 42.37, 32.10, 28.48, 27.18, 21.34, 13.63. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{30}N_3O_4$, 472.2236; found, 472.2231.

Ethyl 2'-amino-5-chloro-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5b)

White solid, m.p. >300 ^{o}C, yield: 0.455 g, 90%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 9.93 (s, 1H), 7.42 (t, *J* = 7.6 Hz, 4H), 7.11 – 6.97 (m, 3H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 3.79 – 3.61 (m, 2H), 2.43 (s, 3H), 2.10 (m, 2H), 1.81 (m, 2H), 0.88 – 0.80 (m, 6H), 0.74 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 193.99, 182.23, 169.13, 153.21, 150.98, 144.07, 139.90, 138.21, 133.97, 127.18, 123.09, 120.64, 113.17, 108.06, 79.50, 58.87, 50.65, 49.16, 42.35, 32.07, 28.88, 26.76, 21.33, 13.61. **HRMS** (ESI-TOF) m/z: $[M + H]^{+}$ calcd for $C_{28}H_{29}ClN_3O_4$, 506.1846; found, 506.1844.

2'-Amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5c)

White solid, m.p. >300 ^{o}C, yield: 0.402 g, 95%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.23 (s, 1H), 7.39 (m, *J* = 7.4Hz, 4H), 7.14 (m, *J* = 8.2 Hz, 2H), 6.95 – 6.89 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 5.34 (s, 2H), 2.42 (s, 3H), 2.12 (m, 2H), 1.89 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.35, 179.98, 152.53, 151.68, 141.90, 140.03, 137.19, 133.75,131.25, 128.13, 123.63, 121.86, 119.46, 110.75, 109.30, 61.20, 56.50, 49.78, 48.94, 41.81, 32.57, 28.74, 27.08, 21.31 . **HRMS** (ESI-TOF) m/z: $[M + H]^{+}$ calcd for $C_{26}H_{25}N_4O_2$, 425.1977; found, 425.1974.

2'-Amino-5-chloro-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5d)

White solid, m.p. >300 ºC, yield: 0.435 g, 95%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.37 (s, 1H), 7.57 – 7.24 (m, 5H), 7.17 (m, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.43 (s, 2H), 2.42 (s, 3H), 2.07 (m, 2H), 1.95 (m, 2H), 0.89 (s, 3H), 0.85 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.55, 179.80, 153.07, 151.78, 141.00, 140.07, 139.24, 133.54, 131.22, 130.21, 127.99, 125.88, 123.79, 119.30, 110.65, 110.00, 60.31, 49.65, 49.48, 41.83, 32.61, 28.31, 27.59, 21.32. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{24}ClN_4O_2$, 459.1587; found, 459.1582.

Ethyl 2'-amino-1'-(4-fluorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5e)

White solid, m.p. >300 ºC, yield: 0.389 g, 82%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 9.94 (s, 1H), 8.01 (d, *J* = 8.3 Hz, 2H), 7.76 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 7.2 Hz, 3H), 7.03 (t, *J* = 7.6 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 3.70 (s, 2H), 2.17 – 2.06 (m, 2H), 1.79 (m, 2H), 0.87 – 0.80 (m, 6H), 0.75 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.06, 182.08, 169.18, 152.91, 150.13, 144.12, 138.08, 131.93, 130.67, 130.42, 127.95, 127.26, 123.18, 120.65, 113.51, 108.12, 79.79, 58.97, 50.67, 49.19, 42.35, 32.16, 28.80, 26.71, 13.59. **^{19}F NMR (471 MHz, DMSO-d^{6}) δ** -111.35. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{27}FN_3O_4$, 476.1985; found, 476.1987.

Ethyl 2'-amino-7',7'-dimethyl-1'-(3-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5f)

White solid, m.p. >300 ^{o}C, yield: 0.421 g, 84%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 9.96 (s, 1H), 8.46 (d, *J* = 7.2 Hz, 2H), 8.01 – 7.85 (m, 2H), 7.38 – 7.13 (m, 3H), 7.03 (m, *J* = 7.6, Hz, 1H), 6.85 – 6.76 (m, 1H), 6.65 (t, *J* = 7.9 Hz, 1H), 3.74 – 3.67 (m, 2H), 2.17 – 2.00 (m, 2H), 1.81 (m, 2H), 0.85 (d, 3H), 0.82 (d, 3H), 0.75 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.16, 182.11, 169.23, 153.00, 150.25, 144.09, 137.70, 132.07, 127.25, 126.40, 125.36, 120.64, 113.46, 108.06, 79.81, 59.32, 59.00, 56.50, 50.68, 49.19, 42.38, 32.20, 28.84, 26.71, 13.59. **HRMS** (ESI-TOF) m/z: $[M + H]^{+}$ calcd for $C_{27}H_{27}N_4O_6$, 503.1930; found, 503.1934.

Ethyl 2'-amino-5-chloro-7',7'-dimethyl-1'-(3-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5g)

White solid, m.p. >300 ^{o}C, yield: 0.428 g, 80%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.12 (s, 1H), 8.45 (m, *J* = 8.6 Hz, 1H), 7.90 (t, *J* = 8.0 Hz, 2H), 7.46 – 6.87 (m, 5H), 6.65 (t, *J* = 7.8 Hz, 1H), 3.71 (m, 2H), 2.07 (m, 2H), 1.98 – 1.80 (m, 2H), 0.84 (s, 6H), 0.78 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.35, 181.88, 169.11, 153.12, 150.74, 143.61, 143.36, 137.70, 137.53, 132.92, 131.99, 126.97, 125.41, 124.71, 111.53, 109.20, 78.94, 59.09, 50.56, 49.69, 42.43, 32.21, 28.49, 27.13, 13.61. **HRMS** (ESI-TOF) m/z: $[M + H]^{+}$ calcd for $C_{27}H_{26}ClN_4O_6$, 537.1540; found, 537.1543.

Ethyl 2'-amino-7',7'-dimethyl-1'-(4-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5h)

White solid, m.p. >300 ºC, yield: 0.426 g, 85%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 9.95 (s, 1H), 8.46 (d, *J* = 8.2 Hz, 2H), 7.84 (d, *J* = 7.6 Hz, 2H), 7.26 – 7.10 (m, 3H), 7.03 (m, *J* = 7.6 Hz, 1H), 6.79 (m, *J* = 7.2 Hz, 1H), 6.65 (d, *J* = 7.6 Hz, 1H), 3.70 (t, 2H), 2.12 – 2.07 (m, 2H), 1.81 (m, 2H), 0.84 (m, 6H), 0.75 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.07, 182.24, 169.19, 152.76, 149.95, 144.08, 142.73, 138.12, 132.64, 127.30, 125.99, 123.33, 121.52, 120.65, 113.47, 108.13, 79.89, 59.01, 50.71, 48.97, 42.22, 32.21, 28.82, 26.67, 13.59. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{27}N_4O_6$, 503.1930; found, 503.1929.

2'-Amino-7',7'-dimethyl-1'-(4-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5i)

White solid, m.p. >300 ºC, yield: 0.400 g, 88%,**^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.23 (s, 1H), 8.42 (m, *J* = 7.8 Hz, 2H), 7.80 (d, *J* = 8.7 Hz, 2H), 7.22 (d, *J* = 7.8 Hz, 1H), 7.16 – 7.11 (m, 1H), 6.93 (m, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 7.2 Hz, 1H), 5.67 (s, 2H), 2.22 – 2.11 (m, 2H), 1.89 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.41, 179.82, 151.28, 148.58, 142.39, 141.97, 137.00, 132.51, 128.20, 126.37, 125.88, 123.73, 121.84, 119.23, 111.13, 109.33, 61.61, 49.86, 49.02, 41.82, 32.70, 28.69, 26.99. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}N_5O_4$, 456.1671; found, 456.1669.

2'-Amino-5-bromo-7',7'-dimethyl-1'-(4-nitrophenyl)-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5j)

White solid, m.p. >300 ºC, yield: 0.459 g, 86%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.55 (s, 1H), 7.59 – 6.60 (m, 9H), 2.21 – 2.06 (m, 4H), 1.03 (s, 6H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 195.56, 178.14, 165.09, 159.36, 141.94, 137.28, 134.79, 131.40, 120.15, 119.68, 117.68, 111.66, 110.67, 108.19, 62.43, 57.21, 50.48, 47.53, 45.49, 44.31, 32.46, 28.05, 27.65. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}BrN_5O_4$, 534.0776; found, 534.0772.

Ethyl 2'-amino-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5k)

White solid, m.p. >300 ºC, yield: 0.407 g, 83%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 9.94 (s, 1H), 7.77 – 7.63 (m, 3H), 7.49 (s, 1H), 7.16 (s, 2H), 7.02 (m, *J* = 7.6 Hz, 1H), 6.81 – 6.75 (m, 1H), 6.64 (d, *J* = 7.6 Hz, 1H), 3.74 – 3.64 (m, 2H), 2.19 – 2.05 (m, 2H), 1.80 (m, 2H), 0.84 (m, 6H), 0.75 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.08, 182.15, 169.18, 152.99, 150.39, 145.62, 144.67, 144.05, 138.07, 138.01, 132.22, 130.86, 130.67, 127.22, 120.64, 108.04, 75.07, 58.94, 50.65, 49.14, 42.29, 32.14, 28.87, 26.75, 13.60. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{27}ClN_3O_4$, 492.1690; found, 492.1688.

Ethyl 2'-amino-5-chloro-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5l)

White solid, m.p. >300 ºC, yield: 0.431 g, 82%,**^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.10 (s, 1H), 8.02 – 7.59 (m, 4H), 7.36 (d, *J* = 8.6 Hz, 3H), 7.12 – 7.03 (m, 1H), 6.64 (t, *J* = 7.6 Hz,

1H), 3.84 – 3.59 (m, 2H), 2.15 – 2.01 (m,2H), 1.94 – 1.76 (m, 2H), 0.88 – 0.85 (m, 3H), 0.85 – 0.81 (m, 3H), 0.79 (d, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.28, 181.92, 169.05, 153.09, 150.87, 143.34, 140.35, 137.80, 132.13, 130.99, 130.70, 129.73, 126.97, 124.69, 109.20, 78.76, 59.04, 50.53, 49.67, 42.31, 32.16, 28.48, 27.22, 13.61. **HRMS** (ESI-TOF) m/z: [M + H]+ calcd for C27H26Cl2N3O4, 526.1300; found, 526.1299.

2'-Amino-5-chloro-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro [indoline-3,4'-quinoline]-3'-carbonitrile (5m)

White solid, m.p. >300 ^{o}C, yield: 0.390 g, 83%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.70 – 7.56 (m, 3H), 7.42 (s, 2H), 7.17 (m, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.68 (s, 2H), 2.14 – 1.82 (m, 4H), 0.90 (s, 3H), 0.85 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.62, 179.79, 152.57, 151.60, 140.98, 139.15, 137.59, 131.99, 130.95, 130.69, 129.63, 128.00, 125.93, 119.28, 110.59, 60.39, 49.67, 49.52, 41.78, 32.66, 28.31, 27.59. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}Cl_2N_4O_2$, 479.1041; found, 479.1039.

2'-Amino-5-bromo-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5n)

White solid, m.p. >300 ^{o}C, yield: 0.443 g, 85%, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.38 (s, 1H), 7.96 – 7.27 (m, 6H), 6.73 (d, *J* = 7.6 Hz, 1H), 5.68 (s, 2H), 2.14 – 1.84 (m, 4H), 0.90 (s, 3H), 0.86 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.65, 179.67, 152.59, 151.66, 141.41, 139.53, 137.57, 134.74, 132.00, 130.94, 130.87, 130.70, 129.63, 119.28, 113.71, 111.18, 60.38, 49.66, 49.50, 41.79, 32.67, 28.26, 27.61. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}BrClN_4O_2$, 523.0536; found, 523.0532.

2'-Amino-5-chloro-7',7'-dimethyl-2,5'-dioxo-1'-(4-(trifluoromethyl)phenyl)-5',6',7',8'-tetrahydro-1' H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5o)

White solid, m.p. >300 ºC, yield: 0.450 g, 88%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.36 (s, 1H), 7.97 (d, *J* = 8.2 Hz, 4H), 7.31 (s, 1H), 7.17 (m, *J* = 8.0, 1H), 6.79 (d, *J* = 7.2 Hz, 1H), 5.68 (s, 2H), 2.31 – 1.72 (m, 4H), 0.87 (d, 6H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.62, 179.73, 152.35, 151.54, 141.04, 140.01, 139.12, 131.91, 128.03, 127.79, 125.91, 123.90, 119.19, 110.67, 110.29, 60.55, 49.69, 49.54, 41.83, 32.68, 28.27, 27.51. **^{19}F NMR (471 MHz, DMSO-d^{6}) δ** -111.41. **HRMS** (ESI-TOF) m/z: [M + H]+ calcd for $C_{26}H_{21}ClF_3N_4O_2$, 513.1305; found, 513.1303.

2'-Amino-5-bromo-7',7'-dimethyl-2,5'-dioxo-1'-(4-(trifluoromethyl)phenyl)-5',6',7',8'-tetrahydro-1' H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5p)

White solid, m.p. >300 ºC, yield: 0.490 g, 88%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.37 (s, 1H), 7.97 (d, *J* = 8.3 Hz, 2H), 7.75 (d, *J* = 8.6Hz, 2H), 7.42 (d, *J* = 7.6 Hz, 1H), 7.30 (m, *J* = 8.2 Hz, 1H), 6.74 (d, *J* = 8.2 Hz, 1H), 5.69 (s, 2H), 2.05 (m, 4H), 0.89 (s, 3H), 0.84 (d, 3H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.62, 179.58, 152.35, 151.53, 141.48, 140.00, 139.51, 131.92, 130.89, 127.79, 126.57, 119.20, 113.65, 111.24, 110.29, 108.42, 60.56, 49.69, 49.53, 41.83, 32.70, 28.24, 27.55. **^{19}F NMR (471 MHz, DMSO-d^{6}) δ** -111.43. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{21}BrF_3N_4O_2$, 557.0799; found, 557.0797.

2'-Amino-7',7'-dimethyl-2,5'-dioxo-1'-(4-(trifluoromethyl)phenyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile(5q)

White solid, m.p. >300 ºC, yield: 0.420 g, 88%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.20 (s, 1H), 7.44 (t, *J* = 8.3 Hz, 4H), 7.23 – 7.10 (m, 2H), 6.91 (m, *J* = 7.6 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.51 (s, 2H), 2.10 (m, 2H), 1.89 (d, 2H), 0.90 (s, 3H), 0.82 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.36, 179.94, 152.43, 151.75, 141.93, 137.16, 134.71, 133.82, 132.96, 129.97, 128.13, 123.68, 123.59, 121.82, 110.91, 109.28, 60.15, 49.79, 48.94, 41.83, 32.56, 28.74, 27.06. **^{19}F NMR (471 MHz, DMSO-d^{6}) δ** -111.42. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{22}F_3N_4O_2$, 479.1694; found, 479.1696.

2'-Amino-1'-(4-methoxyphenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5r)

White solid, m.p. >300 ºC, yield: 0.436 g, 92%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.21 (s, 1H), 7.38 (m, *J* = 7.6 Hz, 1H), 7.18 – 7.10 (m, 4H), 6.91 (t, *J* = 7.8 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.38 (s, 2H), 3.85 (s, 3H), 2.12 (m, 2H), 1.89 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.37, 180.03, 160.28, 152.86, 151.90, 141.89, 137.24, 128.65, 128.11, 123.64, 121.84, 119.53, 116.08, 112.28, 110.66, 109.28, 60.94, 55.97, 49.75, 48.93, 41.82, 32.54, 28.78, 27.07. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{24}ClN_4O_3$, 475.1536; found, 475.1534.

Ethyl 2'-amino-5-bromo-1'-(4-fluorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5s)

White solid, m.p. >300 ºC, yield: 0.464 g, 84%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.09 (s, 1H), 7.57 (m, 5H), 7.32 – 7.16 (m, 3H), 6.60 (d, *J* = 8.1 Hz, 1H), 3.75 – 3.64 (m, 2H), 2.10 – 2.02 (m, 2H), 1.86 (m, 2H), 0.92 – 0.73 (m, 9H).). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.32, 181.91, 168.83, 153.31, 151.55, 143.36, 140.48, 139.94, 133.78, 130.31, 129.42, 126.93, 124.59, 123.12, 112.46, 111.53, 109.24, 78.38, 58.98, 50.52, 49.68, 42.37, 32.03, 28.48, 27.09, 13.32. **^{19}F NMR (471 MHz, DMSO-d^{6}) δ** -111.36.

2'-Amino-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (5t)

White solid, m.p. >300 ºC, yield: 0.381 g, 86%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.22 (s, 1H), 7.80 – 7.58 (m, 3H), 7.46 (s, 1H), 7.31 – 7.09 (m, 2H), 6.91 (t, *J* = 7.2 Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.59 (s, 2H), 2.10 (t, 2H), 1.87 (m, 2H), 0.90 (s, 3H), 0.82 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 194.19, 179.69, 152.48, 151.68, 141.90, 140.03, 137.19, 133.75, 131.25, 128.13, 123.63, 121.86, 119.46, 110.75, 109.30, 106.29, 90.39, 61.20, 56.50, 49.78, 48.94, 41.81, 32.57, 28.74, 27.22.

Ethyl 2'-amino-5-bromo-1'-(3-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7', 8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5u)

White solid, m.p. >300 ºC, yield: 0.490g, 86%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.12 (s, 1H), 7.70 – 7.17 (m, 7H), 6.60 (d, J = 8.1 Hz, 2H), 3.70 (m, 2H), 2.12 – 2.00 (m, 2H), 1.95 – 1.78 (m, 2H), 0.87 (s, 3H), 0.83 (t, 3H), 0.79 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ**

194.30, 181.60, 169.19, 153.12, 150.74, 143.61, 143.36, 137.70, 137.53, 132.92, 131.99, 126.97, 125.41, 124.71, 111.53, 109.20, 78.67, 59.09, 50.56, 49.69, 42.43, 32.05, 28.49, 27.08, 13.32.

5-((5aR,10bR)-5a-Hydroxy-3,3-dimethyl-1-oxo-5-(p-tolyl)-1,3,4,5,5a,6-hexahydroindolo[2,3-b]indol-10b(2H)-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (7)

White solid, m.p. 225 ^{o}C, yield: 86%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.53 (s, 1H), 10.12 (s, 2H), 7.89 (d, *J* = 8.3 Hz, 1H), 7.85 – 7.68 (m, 1H), 7.66 (s, 1H), 7.46 (d, *J* = 8.0 Hz, 2H), 7.32 (m, *J* = 8.0 Hz, 1H), 7.09 (d, *J* = 7.8 Hz, 2H), 5.97 (s, 1H), 3.02 (d, 3H), 2.43 – 2.06 (m, 4H), 1.13 (s, 6H). 5.98 (s, 1H), 3.35 (br, 1H), 3.03 (d, 3H), 2.43 – 2.08 (m, 4H), 1.14 (s, 6H). **^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 166.52, 159.72, 151.19, 150.05, 147.77, 145.81, 143.58, 135.59, 130.47, 129.29, 128.57, 127.85, 126.94, 125.40, 124.98, 124.55, 119.41, 52.27, 47.51, 32.86, 28.11.

Ethyl (Z)-2-cyano-2-(2-oxoindolin-3-ylidene) acetate (B)

Red solid, m.p. 222 ^{o}C, yield: 86%, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 11.10 (s, 1H), 8.10 (d, *J* = 7.7 Hz, 1H), 7.48 – 7.45 (m, 1H), 7.03 – 6.98 (m, 1H), 6.87 (d, *J* = 7.6 Hz, 1H), 4.41 (d, *J* = 7.1 Hz, 2H), 1.33 (t, *J* = 7.1 Hz, 3H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 166.33, 161.66, 146.51, 145.69, 138.82, 136.53, 129.59, 122.37, 118.96, 111.33, 105.11, 63.37, 14.10.

5.4.3 Spectral data of Product ethyl 2'-amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate (5a)

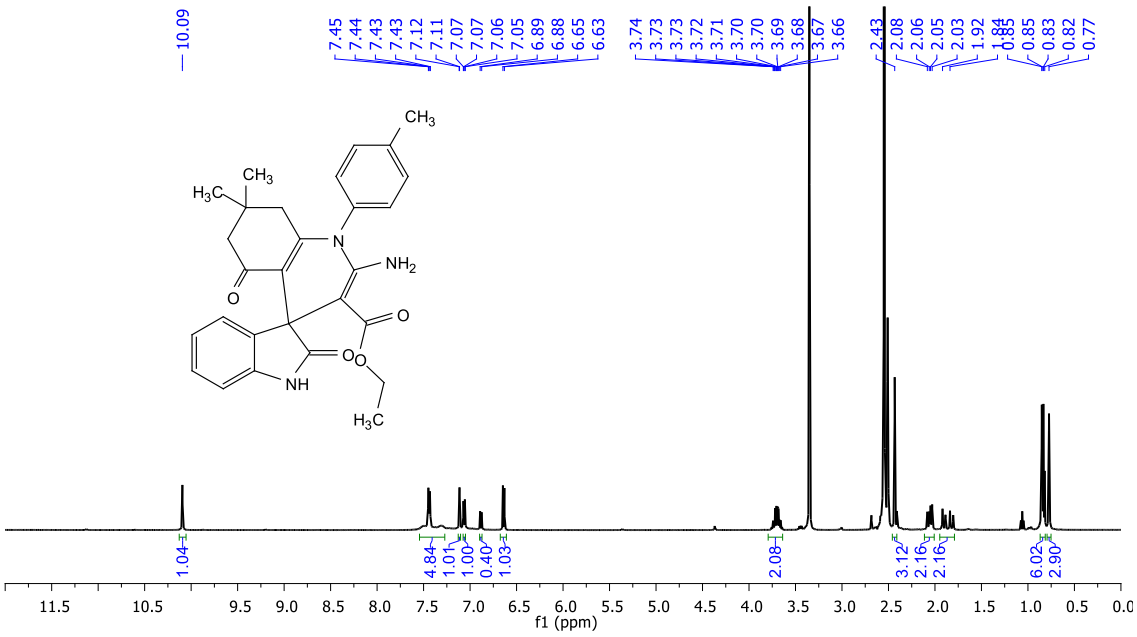


Figure 5.1 ^{1}H NMR **(500 MHz, DMSO-d^{6}) δ** of ethyl 2'-amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate **(5a)**

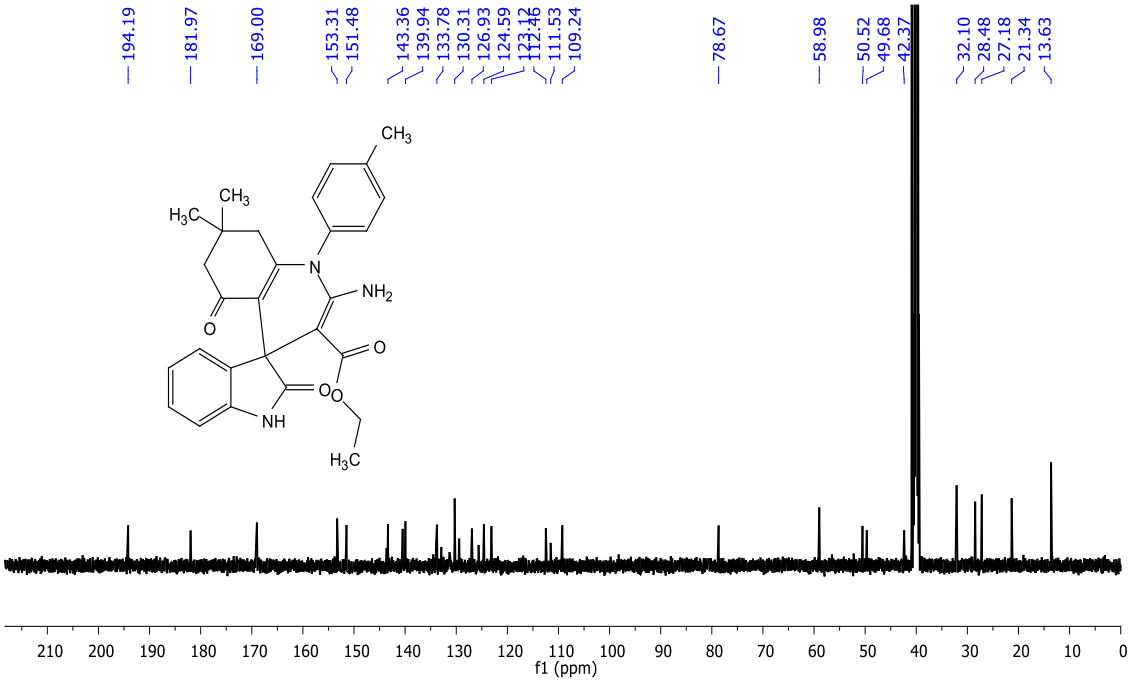


Figure 5.2 ^{13}C NMR of ethyl 2'-amino-7',7'-dimethyl-2,5'-dioxo-1'-(p-tolyl)-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carboxylate **(5a)**

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