CHAPTER 4

VISIBLE -LIGHT TRIGGERED SYNTHESIS OF SPIRO [INDOLINE-3,4'-QUINOLINE] VIA OXIDATIVE COUPLING OF INDOLE WITH ENAMINONE AND MALONONITRILE

Visible-light triggered synthesis of spiro [indoline-3,4'-quinoline] via oxidative coupling of indole with enaminone and malononitrile

4.1 Introduction

In the last few years, there has been a great demand for the effective synthesis of green, environmentally friendly, and metal-free approaches for preparing organic compounds [1]. At this time, chemists are more attracted towards visible light irradiation to synthesize organic compounds due to more valuable demands as it is low cost, environmentally friendly, green, non-toxic, easy to handle, and a renewable energy source [2,3].

Currently, multicomponent synthesis has more advantages for modern organic synthetic chemistry. In multicomponent reactions (MCRs), three or more starting reactants are mixed in one pot and give highly complex molecules in one step. It is easy to separate the compound, reduce time, diminish costs, and provide a good yield compared to multistep synthesis [4,5].

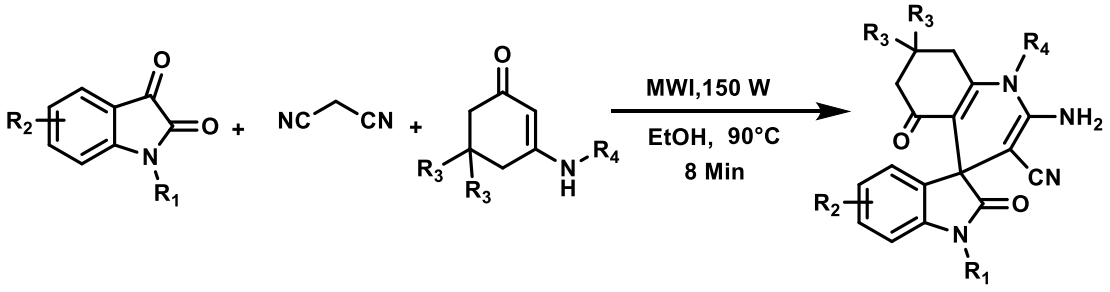
Visible-light-initiated multicomponent synthesis has also attracted considerable attention over the past years for the fast and proficient synthesis of several organic compounds. This approach is more helpful in preparing various chemical libraries, which are usually used for drugs for biological activity [6,7].

Spiro-indolo-quinoline heterocyclic compounds have much more application in medicine [8], natural product [9], agrochemical [10], therapeutic agent [11], bioorganic molecules and also play a vital role in biological activity such as antiasthmatic [12], anti-HIV [13], antihypertensive [14], anti-inflammatory [15], antitumor [16], antituberculosis [17], and antimalarial properties [18]. Various types of naturally occurring plants also have spiroindole heterocyclic compounds. The spiroindoles are a more striking moiety in organic and medicinal chemistry and also show various biological applications in antimycobacterial [19], antitumor [20], antitubercular, antifungal [21], antioxidant agents [22,23] anti-inflammatory, anticancer, analgesic, antimalarial, and antiviral activities. Isatin is important in the heterocyclic compound, having much exciting activity and being used for many chemical transformations [24,25]. The combination of visible light with multicomponent synthesis is an efficient operation to access suitable new organic molecule.

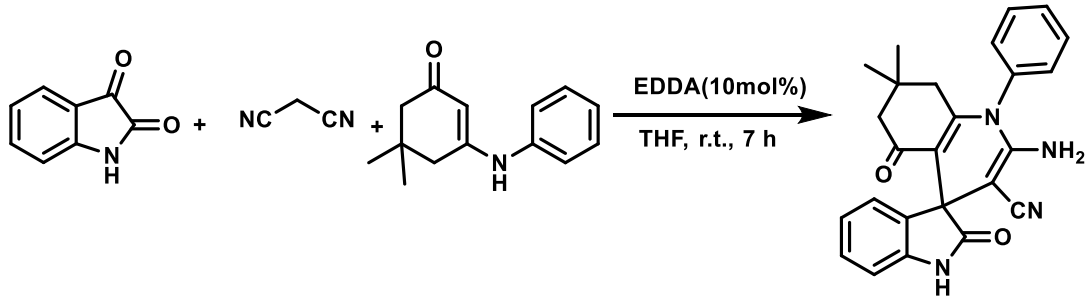
Due to the importance of such a compound, some synthetic protocols for constructing spiro[indoline-3,4'-quinoline] have been reported **(Scheme 4.1)**.

Previous work

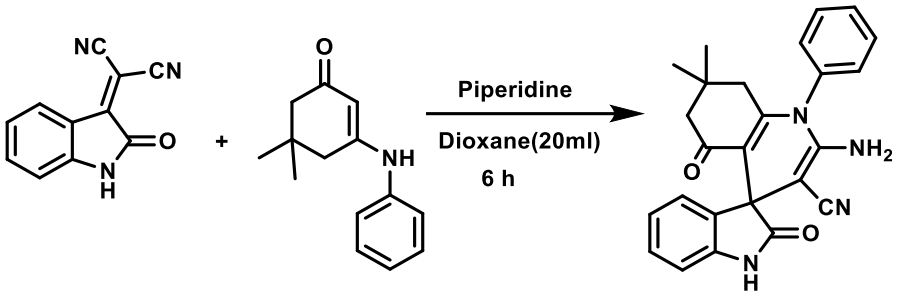
(a) S.-L. Zhu, K. Zhao, X.-M. Su, S.-J. Ji, Synthetic Communications 2009, 39, 1355



(b) S. R. Kang, Y. R. Lee, Synthesis **2013**, 45, 2593

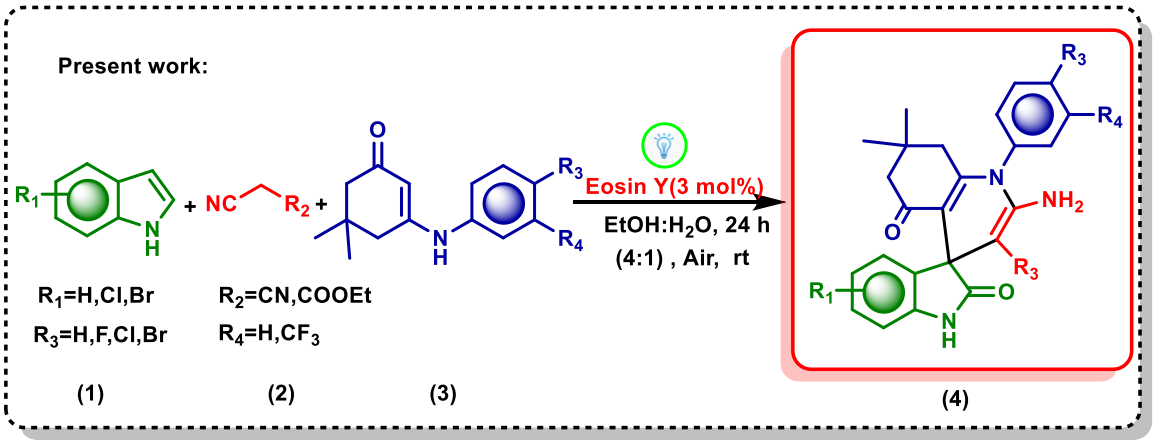


(c) S. A. S. Ghozlan, M. F. Mohamed, A. G. Ahmed, S. A. Shouman, Y. M. Attia, I. A. Abdelhamid, Archiv der Pharmazie **2015**, 348, 113



Scheme 4.1 Synthesis of spiro[indoline-3,4'-quinoline] by previous method

We advocate an appealing design to create a new ecologically friendly organic synthesis approach that uses visible light as its primary energy source [26]. To reduce the negative environmental impact of metal catalysts, we have developed a one-pot, multicomponent synthesis that uses visible light, a photocatalyst, and a green solvent[27]. Here we report multicomponent synthesis of 2'-amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile derivative under visible light irradiation via oxidative coupling of indole with enaminone and active methylene compounds in excellent yield (75-84%) **(Scheme 4.2)**.



Scheme 4.2 Synthesis of Spiro[indoline-3,4-quinoline] Derivatives

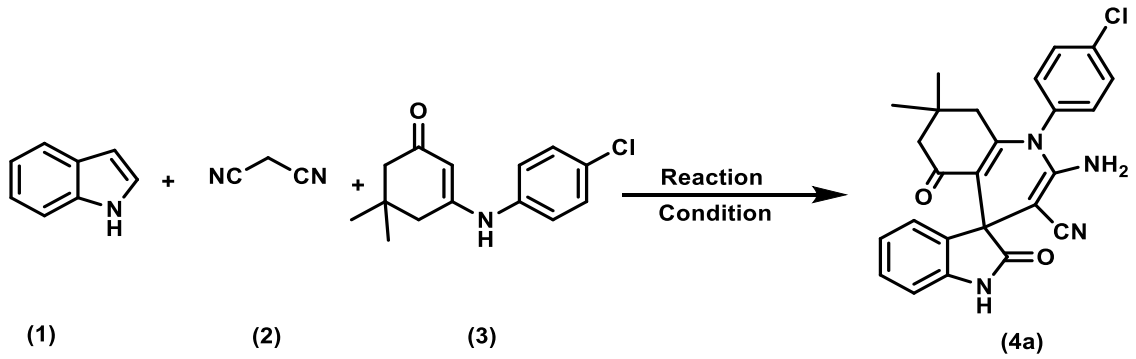
4.2 Results and Discussion

Primarily in our study, we choose a model reaction for carrying out a one-pot multicomponent reaction of indole **1** (1 mmol), malononitrile **2** (1 mmol), and enaminone **3** (1 mmol) in the presence of various catalysts, solvent and LEDs lamps. Firstly, we

investigated the reaction in a different solvents like THF, DMSO, DMF, and CH_3CN under 8W white LED and using eosin Y as a catalyst. We obtained a trace amount of the product after 24 h (**Table 4.1, Entries 1- 4**). Further, a similar reaction was examined in CH_2Cl_2, H_2O, EtOAc, and EtOH in the presence of eosin Y. It was found that ethanol is a superior solvent to others to form the desired product (**Table 4.1, Entries 5-8**). We also investigated the same protocol in the various molar ratio of ethanol and water (2:1, 3:1, 4:1, 5:1), and the product yield was good in 4:1 ratio **(Table 4.1, Entries 9-12)**. Subsequently, after selecting a solvent, we dedicated ourselves to studying the consequence of many visible light sources on the reaction. Now different intensities of LED, such as 8W, 12W, 15W, 20W, and 30W, were optimized under ethanol: water (4:1) system(**Table 4.1, Entries 13-17**). Amazingly, 84% product yield was obtained in 24 h under 22W white LED **(Table 4.1, Entry 16)**. After increasing light intensities, the yield was constant (**Table 4.1, Entry 17**). A similar reaction was carried out in various catalysts like piperidine, ethylenediamine, and trimethylamine were optimized, and 56%, 41%, 28% yields were obtained, respectively (**Table 4.1, Entries 18-20**). Further, we optimized our model reaction using some photocatalysts like rhodamine B and rose bengal and got 27% and 38% yields (**Table 4.1 Entries 21-22**). Unfortunately, there was the formation of only a trace amount of the product in the presence of 8W blue and green LED (**Table 4.1, Entries 23, 24**). However, as soon as the same protocol was performed in the dark for 24h, no product was obtained (**Table 4.1, Entry 25**). The reaction was also tried in sunlight without white LEDs, and we got an 11% yield of product (**Table**

4.1, Entry 26). Finally, we also tried the same procedure for 24 h stirring without white LEDs and did not obtain the expected product (**Table 4.1, Entry 27**).

Table 4.1 Optimization condition for the synthesis of Spiro[indoline-3,4 -quinoline] derivatives **4a**[a]



Entry	Various Conditions For Reaction	Catalyst (3 Mol%)	Solvent	Time (h)	Yield[b] (%)
1.	8 W white LEDs	Eosin Y	THF	24	12
2.	8 W white LEDs	Eosin Y	DMSO	24	9
3.	8 W white LEDs	Eosin Y	DMF	24	11
4.	8 W white LEDs	Eosin Y	CH_3CN	24	12
5.	8 W white LEDs	Eosin Y	CH_2Cl_2	24	11
6.	8 W white LEDs	Eosin Y	H_2O	24	15
7.	8 W white LEDs	Eosin Y	EtOAc	24	9
8.	8 W white LEDs	Eosin Y	EtOH	24	34

9.	8 W white LEDs	Eosin Y	EtOH:H_2O (2:1)	24	54
10.	8 W white LEDs	Eosin Y	EtOH:H_2O (3:1)	24	60
11.	8 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	65
12.	8 W white LEDs	Eosin Y	EtOH:H_2O (5:1)	24	65
13.	12 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	68
14.	15 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	72
15.	20 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	75
16.	**22 W white LEDs**	**Eosin Y**	**EtOH:H_2O (4:1)**	**24**	**84**
17.	30 W white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	84
18.	22 W white LEDs	Piperidine	EtOH:H_2O (4:1)	24	56

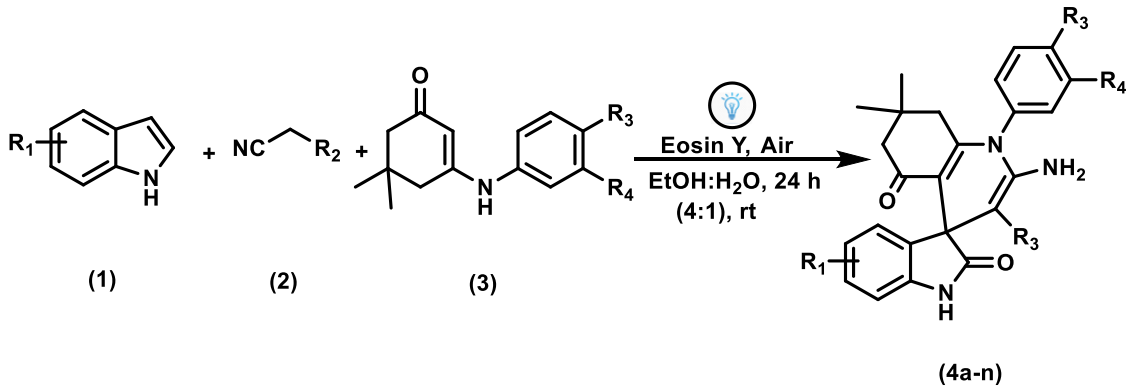
19.	22 W white LEDs	Ethylenediamine	EtOH:H_2O (4:1)	24	41
20.	22 W white LEDs	Triethylamine	EtOH:H_2O (4:1)	24	28
21.	22 W white LEDs	Rhodamine B	EtOH:H_2O (4:1)	24	27
22.	22 W white LEDs	Rose bengal	EtOH:H_2O (4:1)	24	38
23.	22 W white LEDs	Eosin Y	H_2O	24	Trace
24.	8 W blue LEDs	Eosin Y	EtOH:H_2O (4:1)	24	Trace
25.	8 W green LEDs	Eosin Y	EtOH:H_2O (4:1)	24	Trace
26.	Dark	Eosin Y	EtOH:H_2O (4:1)	24	NA
27.	Sunlight instead of white LEDs	Eosin Y	EtOH:H_2O (4:1)	6	11
28.	Stirring without white LEDs	Eosin Y	EtOH:H_2O (4:1)	24	NA

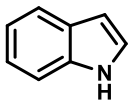
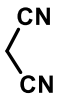
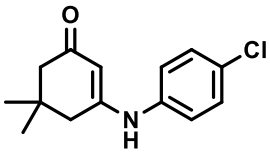
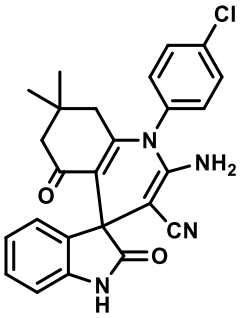
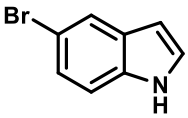
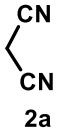
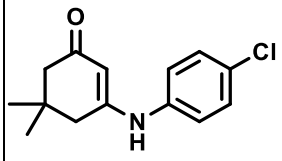
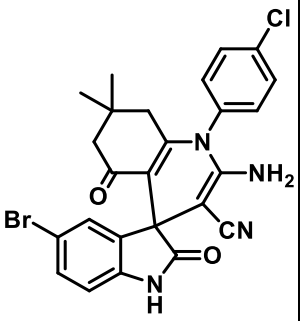
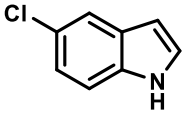
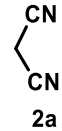
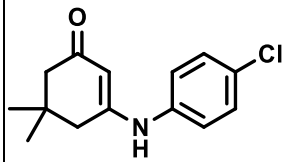
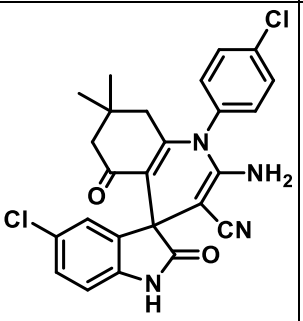
[a]Experimental condition: Indole(1mmol), malononitrile (1mmol), enaminone (1mmol), solvents (5ml) , room temperature,under various visible light irradiation

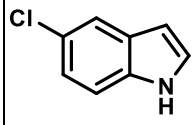
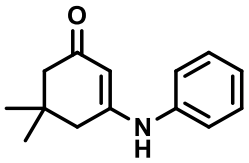
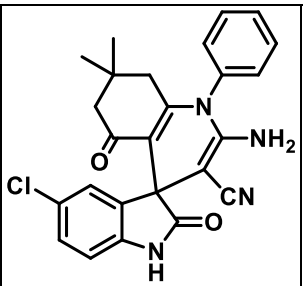
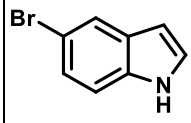
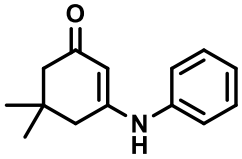
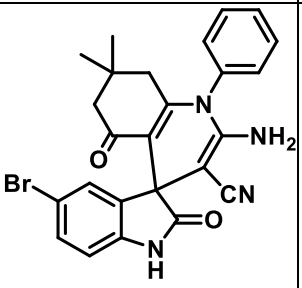
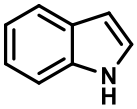
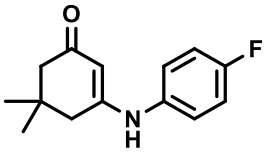
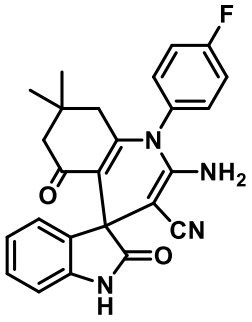
[b] Isolated yields, [c] NA- no reaction

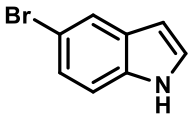
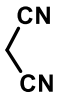
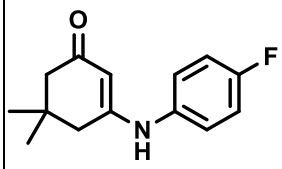
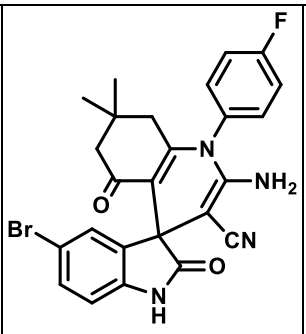
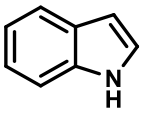
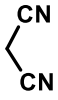
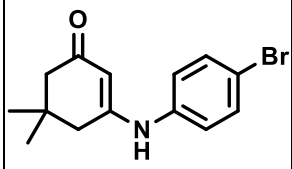
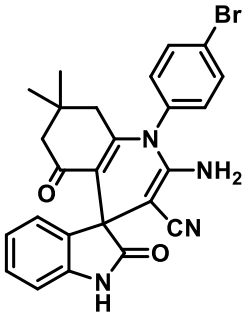
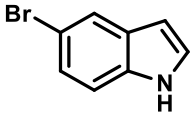
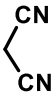
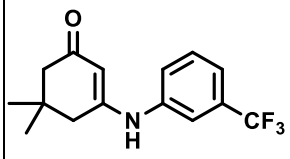
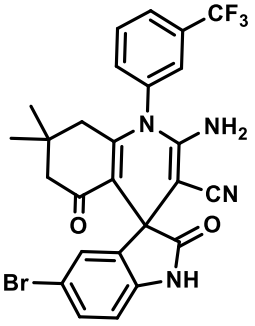
With the aim of extending the opportunity of this approach, various indole **(1a)**, 5-bromoindole **(1b)** and 5-chloroindole **(1c),** active methylene compounds like malononitrile **(2a)** and ethyl cyanoacetate **(2b**) were allowed to react with 3-((4-chlorophenyl)amino)-5,5-dimethylcyclohex-2-en-1-one **(3a)**, 5,5-dimethyl-3-(phenyl- amino)cyclohex-2-en-1-one **(3b)**, 3-((4-fluorophenyl)amino)-5,5-dimethylcyclohex-2-en-1-one **(3c)**, 3-((4-bromophenyl)amino)-5,5-dimethylcyclohex-2-en-1-one **(3d)**, 5,5-dimethyl-3-((3-(trifluoromethyl)phenyl)amino)cyclohex-2-en-1-one **(3e)**, 6-(phenyl- amino)pyrimidine-2,4(1H,3H)-dione **(3f)** and 3-((2-chlorophenyl)amino)-5,5-dimethyl- cyclohex-2-en-1-one **(3g)** under optimal conditions, and the reaction proceeds smoothly in all cases to provide the product (**Table 4.2**).

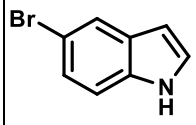
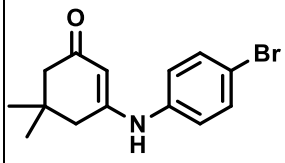
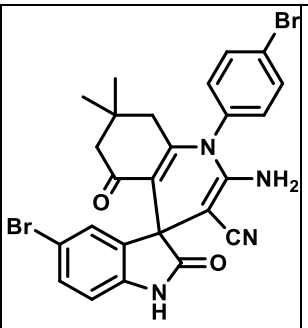
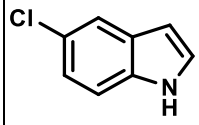
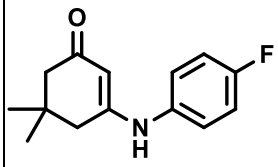
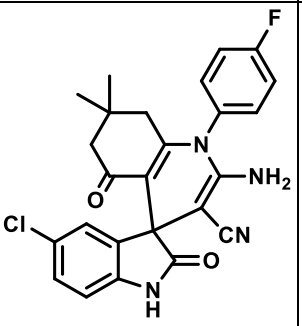
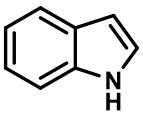
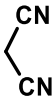
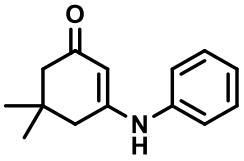
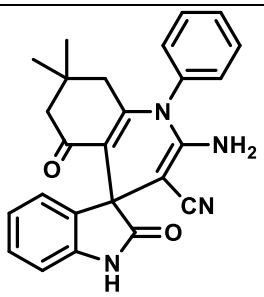
Table 4.2 Library of compounds and versatility of reaction[a]

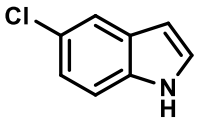
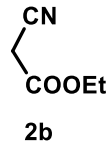
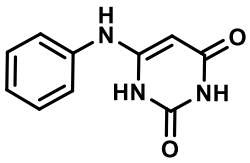
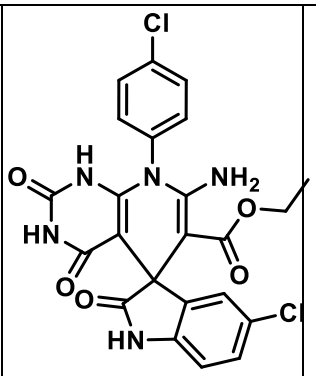
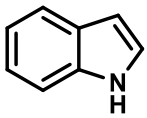
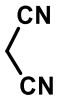
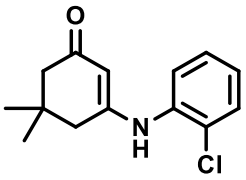
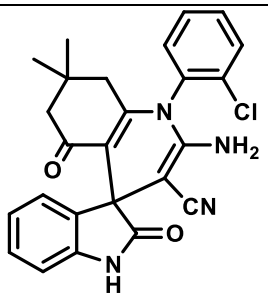


Entry	1	2	3	4[a]	Yield[b] (%)
4a	 1a	 2a	 3a		84
4b	 1b	 2a	 3a		83
4c	 1c	 2a	 3a		80

4d	 **1c**	 **2a**	 **3b**		**78**
4e	 **1b**	 **2a**	 **3b**		**82**
4f	 **1a**	 **2a**	 **3c**		**81**

4g	 **1b**	 **2a**	 **3c**		**80**
4h	 **1a**	 **2a**	 **3d**		**83**
4i	 **1b**	 **2a**	 **3e**		**79**

4j	 **1b**	 **2a**	 **3d**		**82**
4k	 **1c**	 **2a**	 **3c**		**79**
4l	 **1a**	 **2a**	 **3b**		**83**

4m	 **1c**	 **2b**	 **3f**		**74**
4n	 **1a**	 **2a**	 **3g**		**81**

[a]Experimental condition: Indole (1mmol), malononitrile (1mmol), enaminone (1mmol), solvents (5ml), room temperature,under various visible light irradiation ,

[b] Isolated yields,

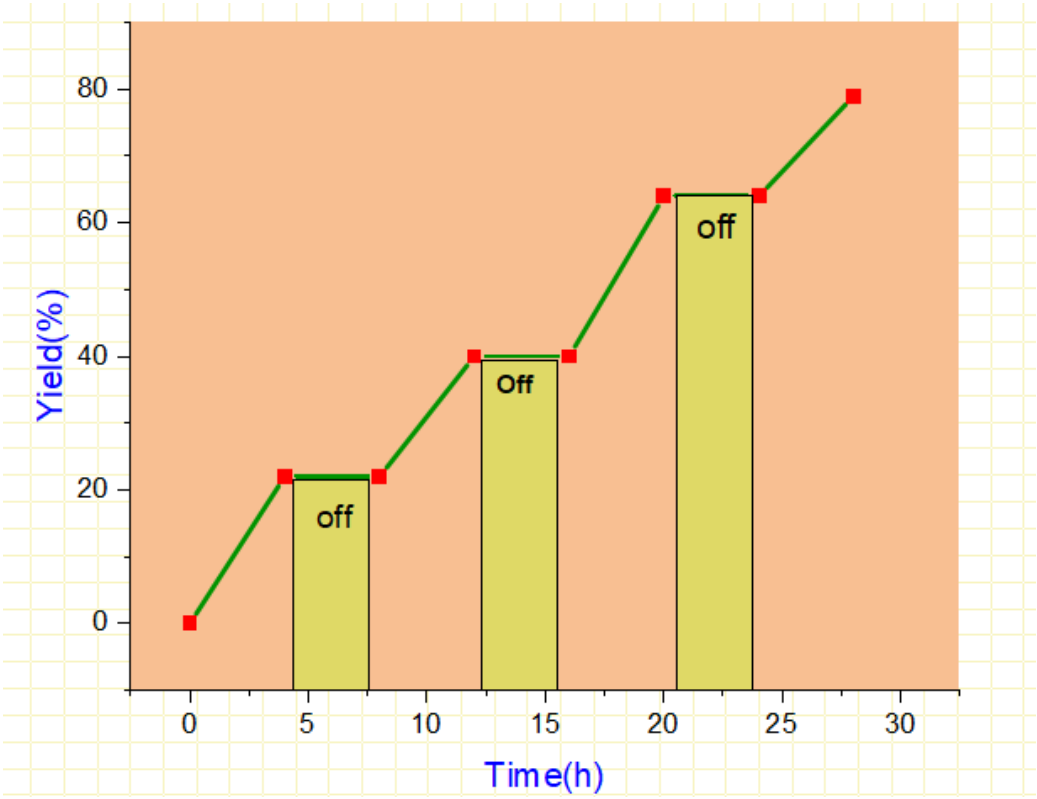
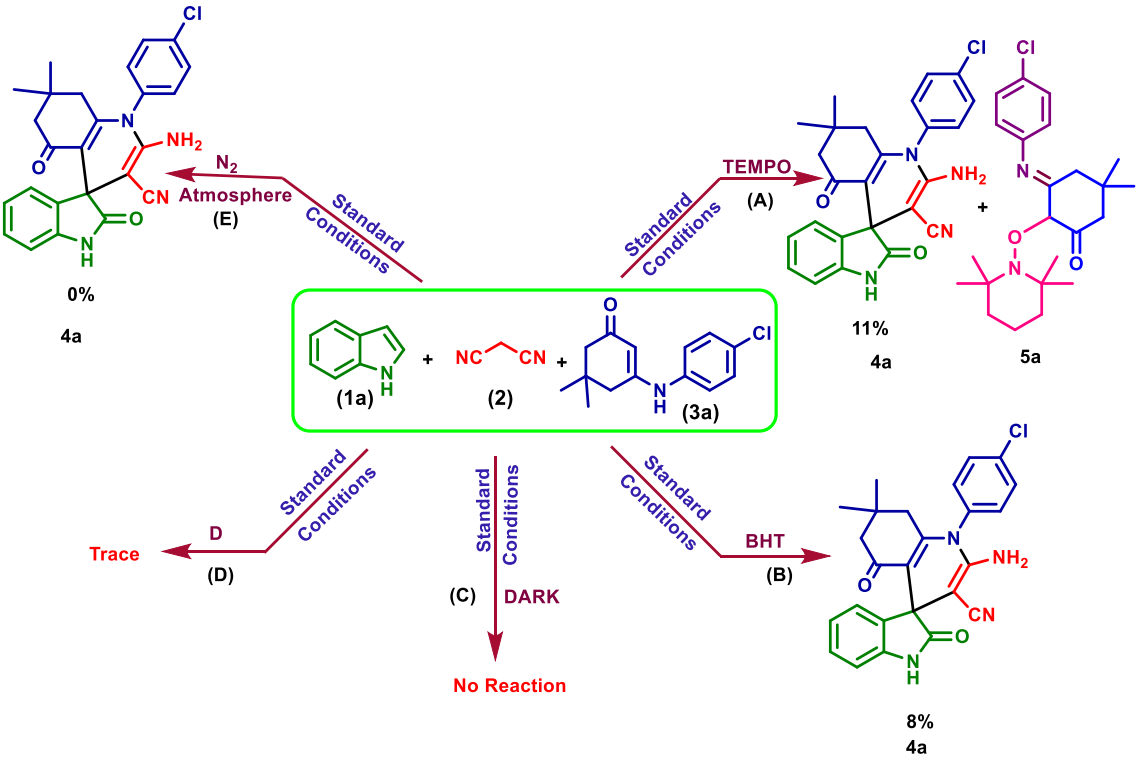


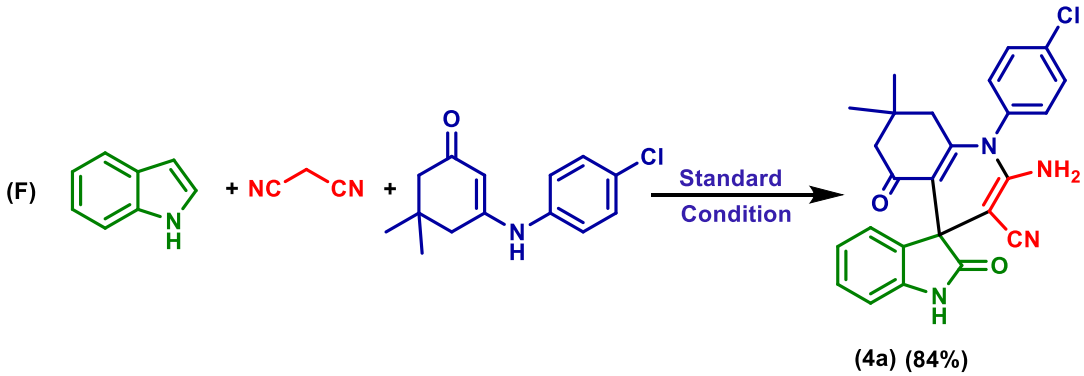
Figure 4.1 The experiment showed the effect of "On-off" switching of the visible light source on reaction

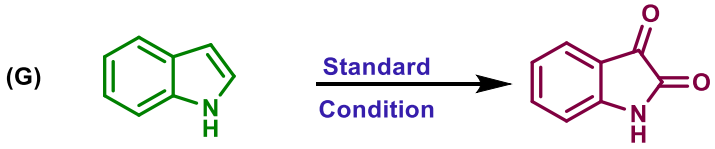
We experimented with mechanistic pathways with a broad substrate scope and optimized reaction conditions, and conducted a few control experiments (**Scheme 4.3**). Initially, we conducted a thermal reaction of indole (1 mmol), malononitrile (1 mmol), and enaminone (1 mmol) in standard conditions and got a trace amount of product, and also no reaction happened when performed in dark conditions. This result confirms the importance of visible light for this reaction. No product was obtained as soon as the reaction was performed in nitrogen. This indicates that there is a role of oxygen in this reaction. Further, radical

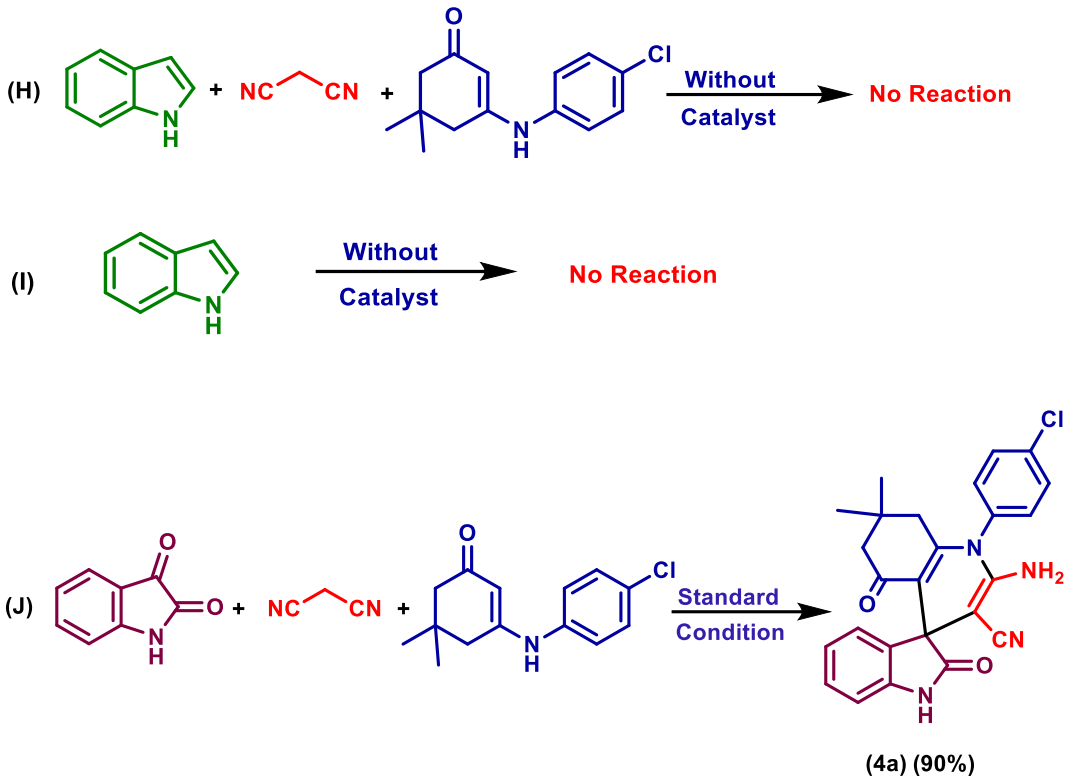
scavengers like TEMPO and BHT were added to the reaction mixture under standard conditions, and the yield of the product spiro [indoline-3,4'-quinoline] was suppressed due to the formation of **5a** (confirmed through HRMS data). This result ensured that the reaction went via a free radical mechanism. The on-off experiment **(Figure 4.1)** was carried out to explore the effect of visible light on the reaction. This experiment shows that the reaction got significantly promoted by visible light irradiation.

More control experiments were conducted to determine the reaction's pathway. Under the standard condition, the reaction of indole (**1a**), malononitrile **(2),** and enaminone **(3a)** were carried out and produced product **4a** in an 84 % yield (**Scheme 4.3, reaction F**). The reaction of indole was carried out under standard conditions alone to identify the intermediate, and the intermediate, isatin (VII), was produced (**Scheme 4.3, reaction G**). By analyzing it using ^{1}H and ^{13}C NMR spectroscopy, the intermediate (VII) production was verified. However, comparable conditions were used for the reaction of isatin (VII) enaminone and malononitrile. The 90% yield of product **4a** (**Scheme 4.3, reaction J**), along with reaction **I**, supports isatin's ability to operate as an intermediate (VII).


Cl
NH2
CN
O
N
H
N2
Atmosphere
(E)
Standard Conditions
0%
4a
TEMPO
(A)
Standard Conditions
11%
4a
5a
(1a)
(2)
(3a)
Standard Conditions
D
Trace
(D)
Standard Conditions
(C)
DARK
No Reaction
Standard Conditions
BHT
(B)
8%
4a


(F)
NC
CN
Cl
Standard
Condition
NH2
CN
(4a) (84%)

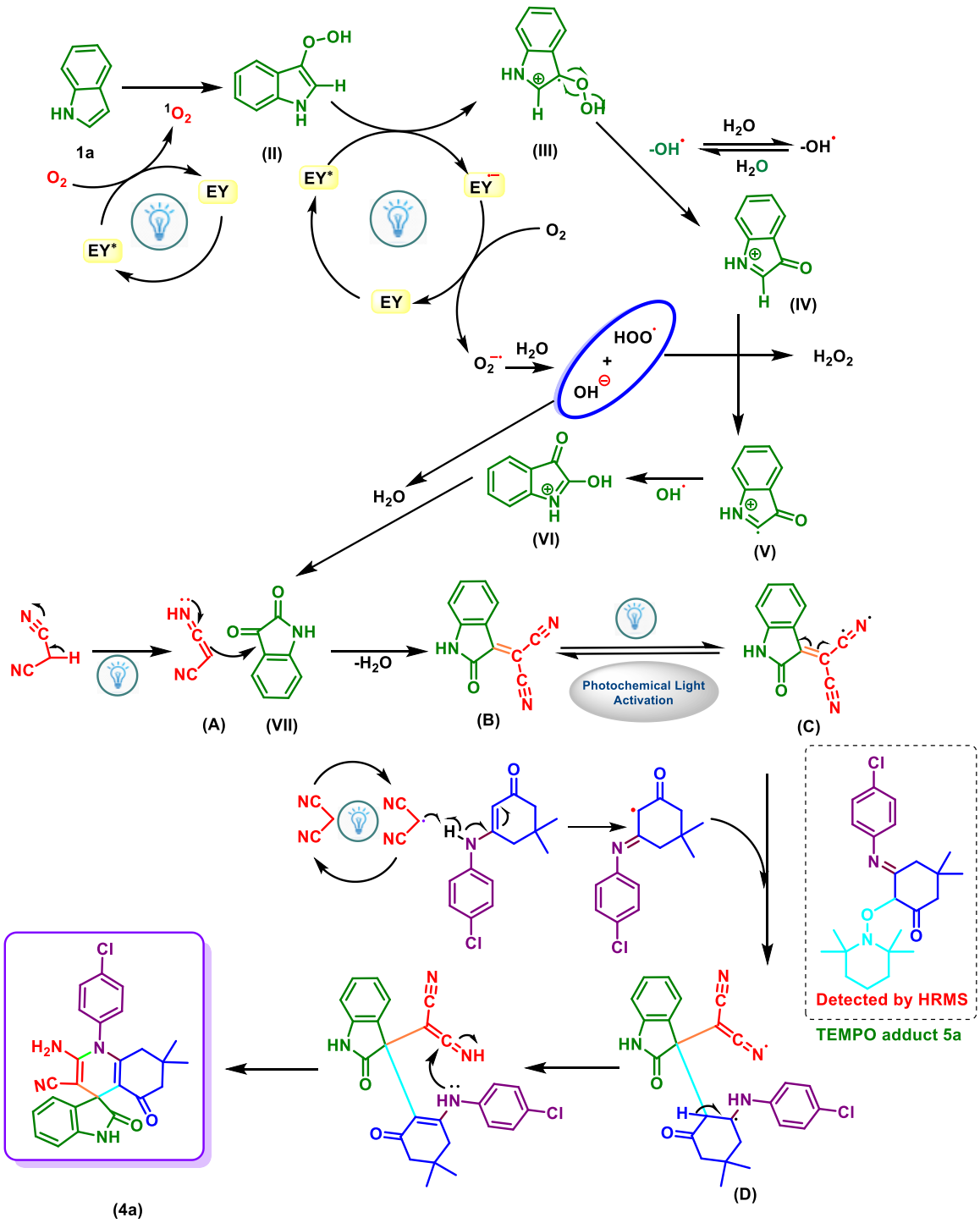

(G)
Standard
Condition



Scheme 4.3 Control experiment for reaction

Based on the study, previous reports, and control experiments, a plausible mechanism was sketched out (**Scheme 4.4**) for this light-promoted three-component reaction [28-30]. Eosin Y was transformed into excited Eosin Y (EY*) when exposed to visible light (EY). Singlet oxygen is created when oxygen quenches the excited form of eosin Y (EY*), which then interacts with indole (I) to create peroxo species (II). In the second photocatalytic cycle, species (II) were oxidised to produce species (III) of peroxoindole and radical anion $EY^{\cdot -}$ By cleaving up different species, the cation (IV) and hydroxyl radical were created one after the other (III). Hydrogen atom from the (IV) is abstracted by the formed hydroxyl radical, which

produces (V). It has been reported that the excited state of eosin Y has an $E^0_{(red)}$ of -1.32 V versus SCE, which is more than enough to reduce oxygen to its superoxide radical anion ($E^0_{(red)}$ is -0.56 V vs SCE). In order to create superoxide radical anion, $EY^{\cdot -}$ reduced oxygen. When the radical anion reacts with water, hydroxide anions and peroxide radicals are produced. The species (VI) (by the release of a water molecule) and the radical species (V) and hydroxyl radical combined to produce the intermediate (VII). Further intermediate (**A)** is formed by the photoexcitation or tautomerization of malononitrile in ethanol. After that, knoevenagel condensation takes place by isatin and intermediate **A** and gives the cyanoolefin intermediate **B** with water removal. The formation of intermediate **B** is confirmed through ^{1}H NMR and ^{13}C NMR spectra. Then this intermediate is activated by visible light to generate a free radical intermediate **C**. The hydrogen of enaminone is acidic, which is abstracted by malononitrile and generates a radical. This radical is rearranged and combined with intermediate **C** to form the intermediate **D** through carbon-carbon bond formation. Consequently, intermediate **D** is intramolecularly cyclized to give the desired product (**4a**).



Scheme 4.4 Proposed reaction mechanism

4.3 Conclusion

We have developed the visible light-mediated multicomponent synthesis of spiro[indoline-3,4'-quinoline] derivative in ethanol using a 22W LED lamp without a catalyst. This present method provides some characteristic profits such as catalyst-free, low cost, environmentally friendly, green, non-toxic, easy to handle, and visible light as a renewable energy source.

4.4 Experimental section

4.4.1 Typical procedure for the preparation of compound (4)

Indole **1** (1.0 mmol), malononitrile **2** (1.0 mmol), and enaminone **3** (1.0 mmol) were stirred at room temperature under visible light irradiation of 22 W white LED in the presence of eosin Y by using ethanol: water (4:1) (5.0 ml) as a solvent. After the completion of the reaction (monitored by TLC), the reaction mixture was filtered and washed with water to yield a solid product. Then, the crude product was recrystallized from ethanol to afford the pure product **4**.

4.4.2 Analytical Data

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

White solid, m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.21 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 2H), 7.51 (s, 2H), 7.18 (d, *J* = 7.3 Hz, 1H), 7.12 (t, *J* = 7.6 Hz, 1H), 6.91 (t, *J* = 7.6

Hz, 1H), 6.76 (d, *J* = 7.6 Hz, 1H), 5.56 (br. s, 2H, NH_2), 2.12 (m,2H), 1.88 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.38, 179.92, 152.15, 151.58, 141.92, 137.12, 135.39, 134.99, 132.47, 130.77, 128.14, 123.69, 121.83, 119.40, 110.94, 109.29, 61.25, 49.79, 48.97, 41.80, 40.49, 40.32, 40.16, 39.99, 39.82, 39.66, 39.49, 32.60, 28.73, 27.04. **IR (KBr, cm^{-1}) :** 3325, 3310 (NH_2), 2175 (CN), 1741 (CO), 1635 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}ClN_4O_2$, 445.1431 ; found,445.1426.

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

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.41 (m, *J* = 7.6 Hz, 6H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.65 (br. s, 2H, NH_2), 2.15 – 1.78 (m, 4H), 0.89 (s, 3H), 0.85 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.59, 179.63, 152.71, 151.66, 141.42, 139.56, 135.16, 135.06, 132.60, 130.85, 130.73, 126.55, 119.26, 113.64, 111.21, 110.15, 60.30, 49.66, 49.48, 41.82, 40.48, 40.32, 40.15, 39.98, 39.82, 39.65, 39.48, 32.64, 28.28, 27.56. **IR (KBr, cm^{-1}) :** 3325, 3316 (NH_2), 2183 (CN), 1738 (CO), 1643 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}BrClN_4O_2$, 523.0536 ; found,523.0533.

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

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 4H), 7.31 – 7.14 (m, 2H), 6.77 (d, *J* = 8.2 Hz, 1H), 5.66 (br. s, 2H, NH_2), 2.19 – 1.75 (m, 4H), 0.89 (s, 3H), 0.85 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.58, 179.77,

152.69, 151.67, 141.00, 139.17, 135.18, 135.06, 132.60, 130.73, 127.99, 125.89, 123.89, 119.26, 110.63, 110.17, 60.32, 49.67, 49.50, 41.82, 40.49, 40.32, 40.15, 39.99, 39.82, 39.65, 39.49, 32.63, 28.32, 27.53. **IR (KBr, cm^{-1}) :** 3328, 3312 (NH_2), 2182 (CN), 1751 (CO), 1648 (CO); **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-chloro-7',7'-dimethyl-2,5'-dioxo-1'-phenyl-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4d)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.76 – 7.34 (m, *J* = 7.8 Hz, 5H), 7.29 – 7.14 (m, 2H), 6.78 (d, *J* = 8.2 Hz, 1H), 5.44 (br. s, 2H, NH_2), 2.14 – 1.83 (m, 4H), 0.88 (s, 3H), 0.84 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.57, 179.77, 152.89, 151.67, 141.02, 139.19, 136.23, 130.74, 130.55, 130.47, 128.01, 125.89, 123.80, 119.24, 110.66, 110.10, 60.48, 56.50, 49.65, 49.50, 41.85, 40.49, 40.41, 40.32, 40.25, 40.16, 39.99, 39.82, 39.66, 39.49, 32.62, 28.26, 27.58. **IR (KBr, cm^{-1}) :** 3328, 3321 (NH_2), 2179 (CN), 1748 (CO), 1639 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}ClN_4O_2$, 445.1431; found, 445.1429.

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

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.37 (s, 1H), 7.79 – 6.59 (m, *J* = 7.8 Hz, 8H), 5.44 (br. s, 2H, NH_2), 2.21 – 1.75 (m, 4H), 1.05 (m, 3H), 0.84 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.57, 179.63, 152.90, 151.66, 141.45, 139.58, 136.21,

130.87, 130.74, 130.54, 130.48, 126.46, 119.24, 113.63, 111.25, 110.09, 60.49, 56.50, 49.65, 49.48, 41.85, 40.50, 40.33, 40.16, 40.00, 39.83, 39.66, 39.50, 32.63, 28.22, 27.62. **IR (KBr, cm^{-1}) :** 3323, 3316 (NH_2), 2190 (CN), 1755 (CO), 1655 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}BrN_4O_2$, 489.0926 ; found, 489.0925.

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

White solid, m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.21 (s, 1H), 7.57 – 7.34 (m, *J* = 7.6 Hz, 4H), 7.29 – 7.00 (m, *J* = 7.4 Hz, 2H), 7.00 – 6.67 (m, 2H), 5.52 (br. s, 2H, NH_2), 2.25 – 2.03 (m, 2H), 1.87 (m, 2H), 0.89 (s, 3H), 0.82 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.38, 179.96, 163.85 (d, J = 251.2 Hz), 161.88, 152.40, 151.72, 141.91, 137.15, 132.69 (dd, J = 13.6, 8.8 Hz), 128.13, 123.70, 121.83, 119.44, 117.62 (d, J = 18.4 Hz), 110.88, 109.28, 61.15, 49.77, 48.96, 41.82, 40.48, 40.31, 40.14, 39.98, 39.81, 39.64, 39.47, 32.56, 28.75, 27.05. **^{19}F NMR (471 MHz, DMSO-d^6) δ** -111.40. **IR (KBr, cm^{-1}) :** 3315, 3310 (NH_2), 2210 (CN), 1740 (CO), 1643 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}FN_4O_2$, 429.1726; found, 429.1724.

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'-carbonitrile (4g)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.92 – 6.61 (m, *J* = 7.9 Hz, 7H), 5.61 (br. s, 2H, NH_2), 2.00 (m, 4H), 1.07 – 0.88 (m, 3H), 0.84 (s, 3H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.59, 179.66, 163.72 (d, J = 260.2 Hz) 152.95, 151.80,

141.42, 139.59, 133.00, 132.45 (d, J = 8.8 Hz), 130.84, 126.54, 119.30, 117.61 (d, J = 18.1 Hz), 111.20, 110.11, 60.22, 49.64, 49.48, 41.83, 40.48, 40.31, 40.15, 39.98, 39.81, 39.65, 39.48, 33.63, 32.60, 31.11, 28.29, 27.57. **^{19}F NMR (471 MHz, DMSO-d^6) δ** -111.36. **IR (KBr, cm^{-1}) :** 3321, 3311 (NH_2), 2193 (CN), 1738 (CO), 1642 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}BrFN_4O_2$, 507.0831; found, 507.0828.

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

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.29 (s, 1H), 7.61 (d, *J* = 7.6 Hz, 4H), 7.42 – 6.94 (m, 3H), 6.72 (d, *J* = 8.1 Hz, 1H), 5.59 (br. s, 2H, NH_2), 2.08 – 1.77 (m, 4H), 0.85 (s, 3H), 0.80 (s, 3H). **IR (KBr, cm^{-1}) :** 3322, 3314 (NH_2), 2175 (CN), 1742 (CO), 1651 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{22}BrN_4O_2$, 489.0926 ; found, 489.0923. Due to less solubility, we are not able to take the ^{13}C NMR .

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

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.46 (d, 1H), 7.97 (t, *J* = 7.5 Hz, 3H), 7.37 (d, *J* = 7.9 Hz, 3H), 6.73 (s, 1H), 5.70 (br. s, 2H, NH_2), 2.00 (d, 4H), 1.01 (s, 3H), 0.85 (d, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.65, 178.16, 165.11, 159.35, 152.53, 141.45, 137.03, 135.10, 131.40 (q, J = 32.2 Hz), 130.87, 126.43 (q, J = 250.2 Hz), 119.26, 115.46, 113.69, 111.66, 111.18, 60.51, 57.19, 50.40, 49.61, 47.52, 40.47, , 40.30, 40.23, 40.14, 39.97, 39.80, 39.63, 39.47, 32.64, 28.00, 27.64. **^{19}F NMR (471 MHz, DMSO-**

d^6) δ -111.43. **IR (KBr, cm^{-1}) :** 3323, 3316 (NH_2), 2190 (CN), 1755 (CO), 1655 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{21}BrF_3N_4O_2$, 557.0799; found, 557.0796.

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

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.30 (s, 1H), 7.61 (s, *J* = 7.8 Hz, 3H), 7.47 – 7.20 (m, *J* = 7.4 Hz, 3H), 6.68 (d, *J* = 7.6 Hz, 1H), 5.59 (br. s, 2H, NH_2), 1.96 (m, 4H), 0.85 (s, 3H), 0.80 (s, 3H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 194.62, 179.67, 152.74, 151.70, 141.49, 139.61, 135.22, 135.11, 132.65, 130.90, 130.78, 126.60, 119.29, 113.68, 111.25, 61.29, 51.16, 49.72, 41.87, 40.56, 40.39, 40.23, 40.06, 39.89, 39.73, 39.56, 32.69, 28.32, 27.62. **IR (KBr, cm^{-1}) :** 3318, 3310 (NH_2), 2180 (CN), 1746 (CO), 1635 (CO); **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}Br_2N_4O_2$, 567.0031; found, 567.0030.

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

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.36 (s, 1H), 7.72 (s, *J* = 7.8 Hz, 1H), 7.47 – 7.37 (m, 4H), 7.30 (m, *J* = 8.2, 1.9 Hz, 1H), 6.74 (t, *J* = 7.3 Hz, 1H), 5.61 (br. s, 2H, NH_2), 2.06 (m, 2H), 1.95 (d, 2H), 0.90 (s, 3H), 0.85 (s, 3H). **^{19}F NMR (471 MHz, DMSO-d^6) δ** -111.42. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{21}ClFN_4O_2$, 463.1337; found, 463.1335. Due to less solubility, we are not able to take the ^{13}C NMR.

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

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.22 (s, 1H), 7.70 – 7.44 (m, *J* = 7.6 Hz, 5H), 7.22 – 7.10 (m, *J* = 7.3 Hz, 2H), 6.95 – 6.76 (m, 2H), 5.34 (br. s, 2H, NH_2), 2.12 (m, 2H), 1.88 (m, 2H), 0.88 (s, 3H), 0.82 (s, 3H). **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{25}H_{23}N_4O_2$, 411.1821; found, 411.1819. Due to less solubility, we are not able to take the ^{13}C NMR.

Ethyl 7'-amino-5-chloro-8'-(4-chlorophenyl)-2,2',4'-trioxo-2',3',4',8'-tetrahydro-1'H-spiro[indoline-3,5'-pyrido[2,3-d]pyrimidine]-6'-carboxylate (4m)

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.09 (s, 1H), 7.70 (d, *J* = 7.4 Hz, 2H), 7.44 (d, *J* = 8.9 Hz, 1H), 7.17 (s, *J* = 7.6 Hz 1H), 6.97 (m, *J* = 7.2 Hz, 3H), 6.64 (br. s, 2H, NH_2), 3.69 (m, 2H), 2.09 – 2.03 (m, 2H), 1.90 (d, 1H), 1.80 (d, 1H), 1.11 – 0.93 (m, 3H), 0.84 (m, 3H), 0.78 (s, 3H). **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{23}H_{18}Cl_2N_5O_5$, 514.0685; found, 514.0681. Due to less solubility, we are not able to take the ^{13}C NMR.

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

White solid , m.p. > 300°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.39 (s, 1H), 7.66 (m, *J* = 7.8 Hz, 7H), 7.27 – 7.06 (m, 4H), 6.98 (d, *J* = 7.3 Hz, 1H), 6.90 (d, *J* = 7.6Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 2H), 2.05 (m, *4*H), 1.04 (s, 3H), 1.00 (s, 3H). **HRMS** (ESI-TOF) m/z: $[M + H]^+$

calcd for $C_{25}H_{22}ClN_4O_2$, 445.1431; found, 445.1429. Due to less solubility, we are not able to take the ^{13}C NMR.

Isatin (intermediate) (VII)

Orange precipitate, m.p. 190°C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 11.22 (s, 1H), 7.90 (d, J=7.8 Hz, 1H), 7.60 (t, J=7.8 Hz, 1H), 7.18 (t, J=7.8 Hz, 1H), 6.90 (d, J=7.7 Hz, 1H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 178.76, 160.35, 149.12, 138.25, 129.86, 128.68, 114.86, 112.56.

4.4.3 Spectral Data of Product 2'-Amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile (4a)

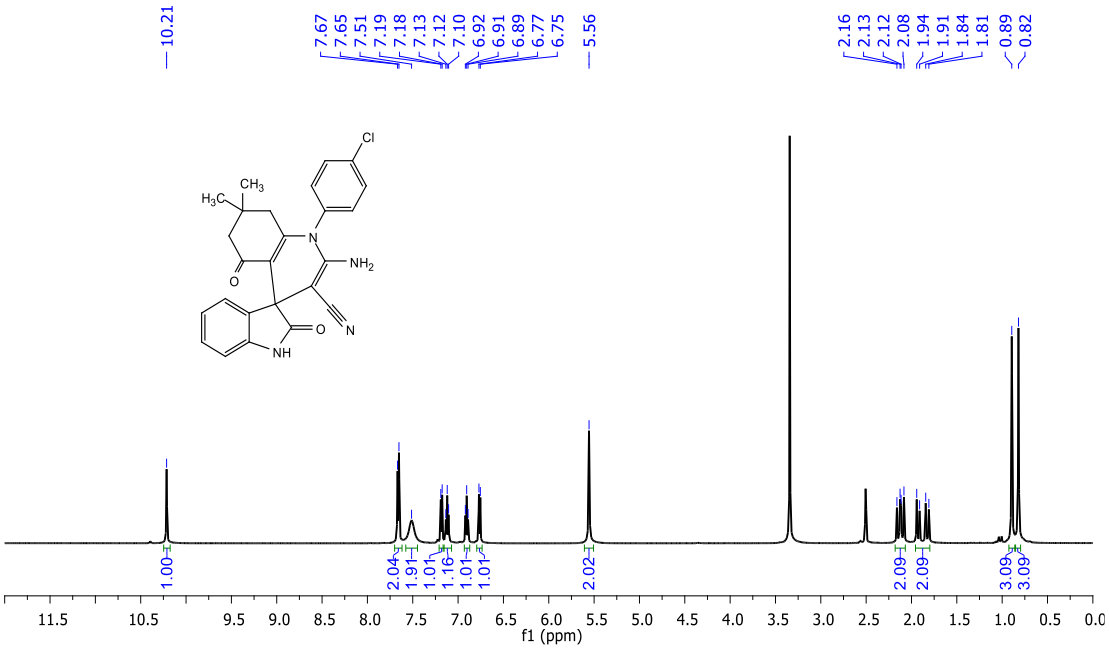


Figure 4.2 ^{1}H NMR 2'-Amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile **(4a)**

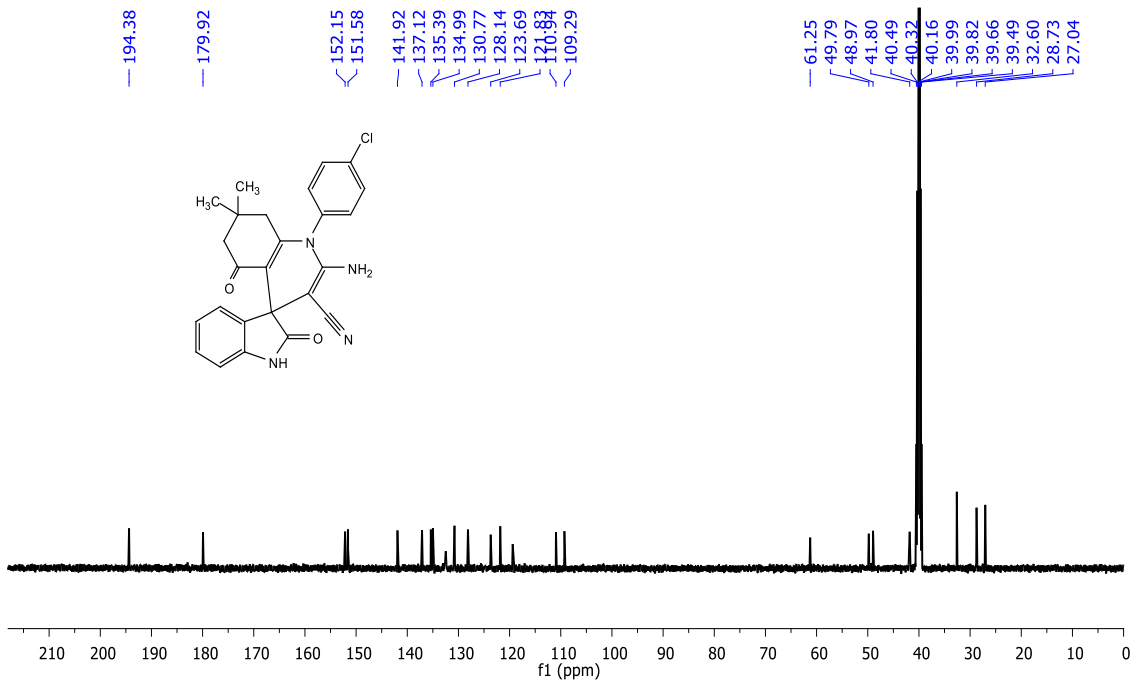


Figure 4.3 ^{13}C NMR 2'-Amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile **(4a)**

4.4.4 Copies of HRMS data of product (4a)

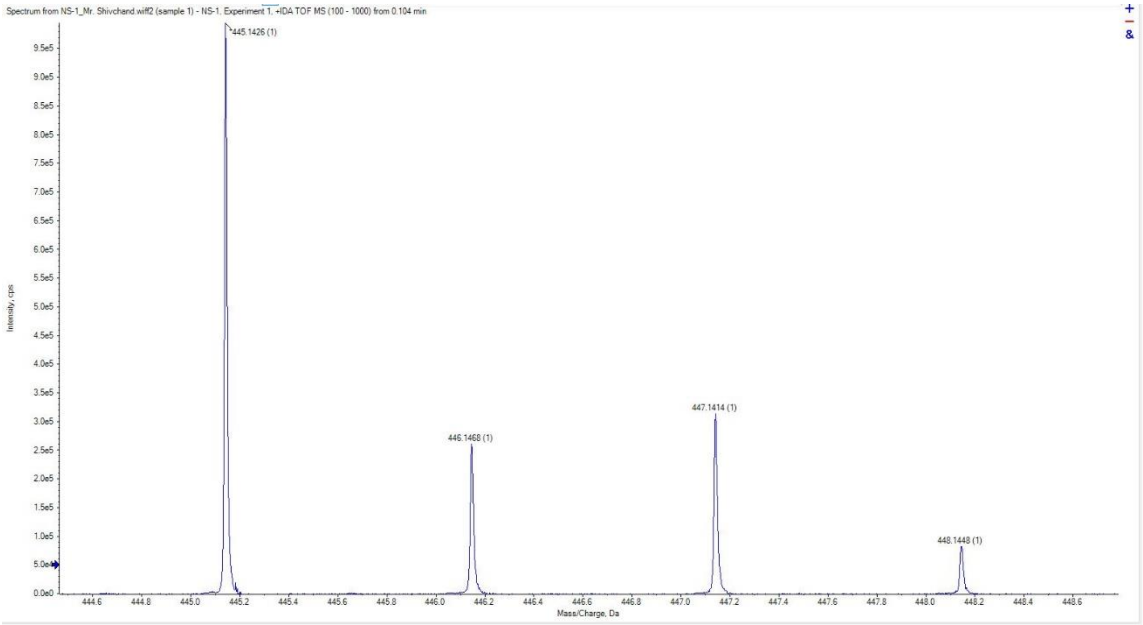


Figure 4.4 HRMS data of 2'-Amino-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile **(4a)**

HRMS data of product (4b)

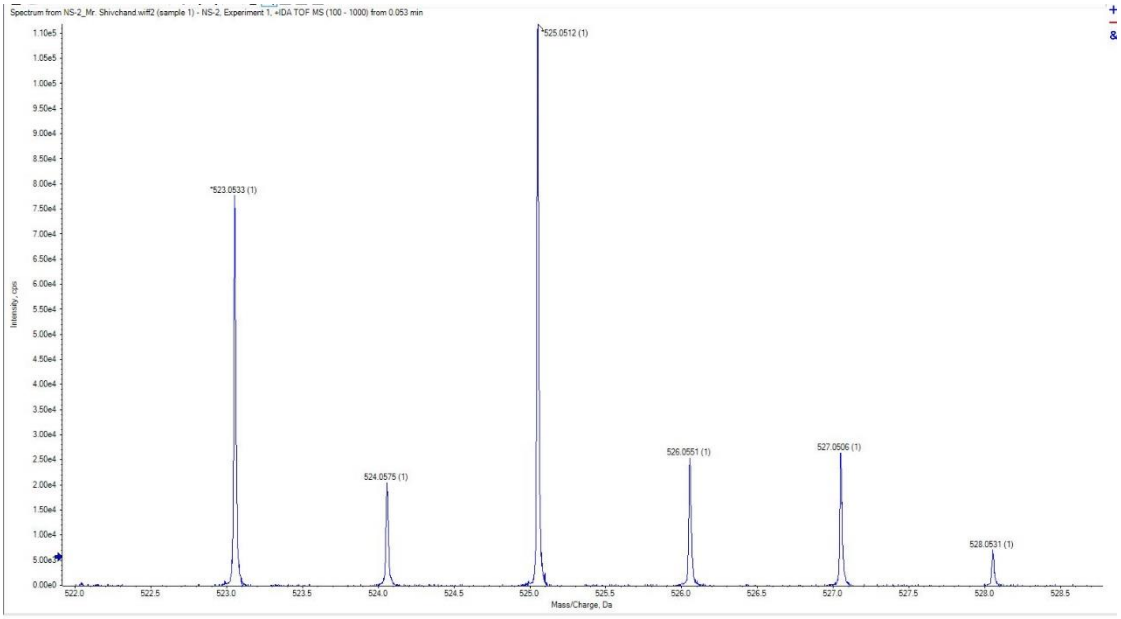


Figure 4.5 HRMS data of 2'-amino-5-bromo-1'-(4-chlorophenyl)-7',7'-dimethyl-2,5'-dioxo-5',6',7',8'-tetrahydro-1'H-spiro[indoline-3,4'-quinoline]-3'-carbonitrile **(4b)**

HRMS data of product (5a)

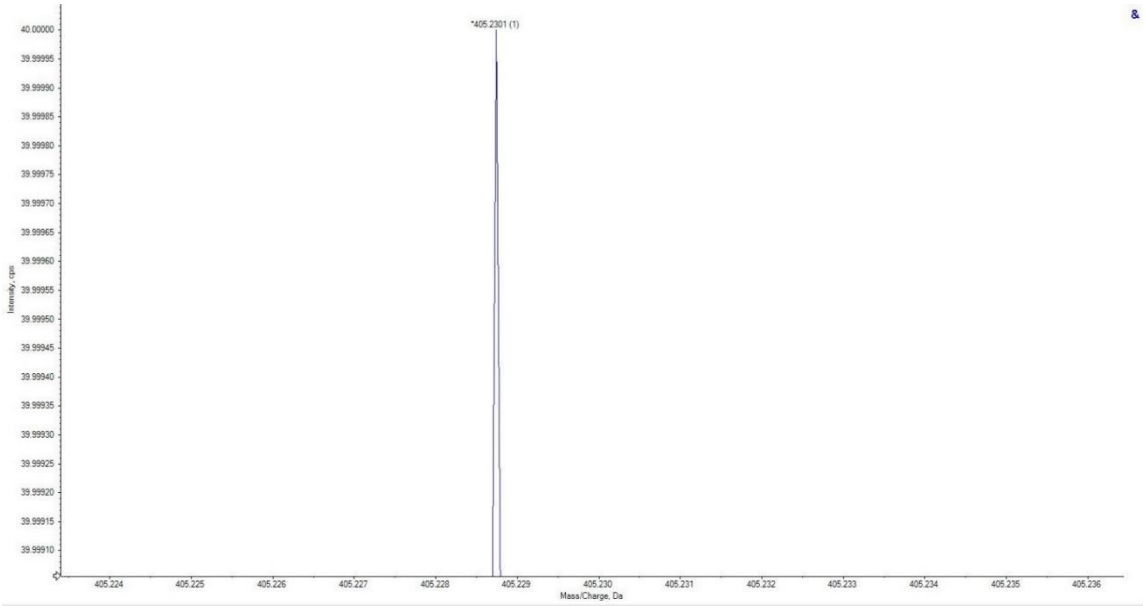


Figure 4.6 HRMS data of (E)-3-((4-chlorophenyl)imino)-5,5-dimethyl-2-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)cyclohexan-1-one **(5a)**

4.4.5 Data of UV-Visible absorption Spectra

UV-visible spectroscopy of reaction solution was recorded on a SHIMADZU UV-1800 UV-visible spectrophotometer. The sample was prepared by mixing of indole, malononitrile, and enaminone derivatives in methanol solvent [Conc. reaction mixture = 1.25×10-4mol/L] in a light path quartz UV cuvette.

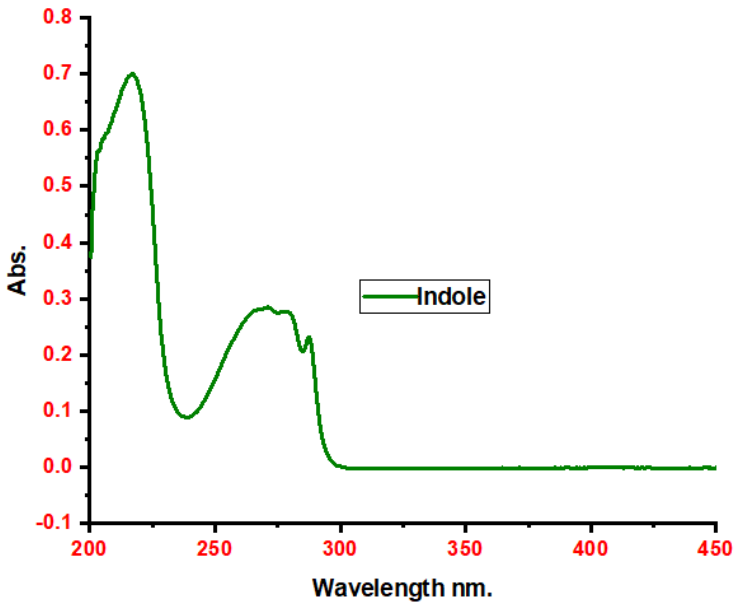


Figure 4.6 UV spectrum of Indole in methanol

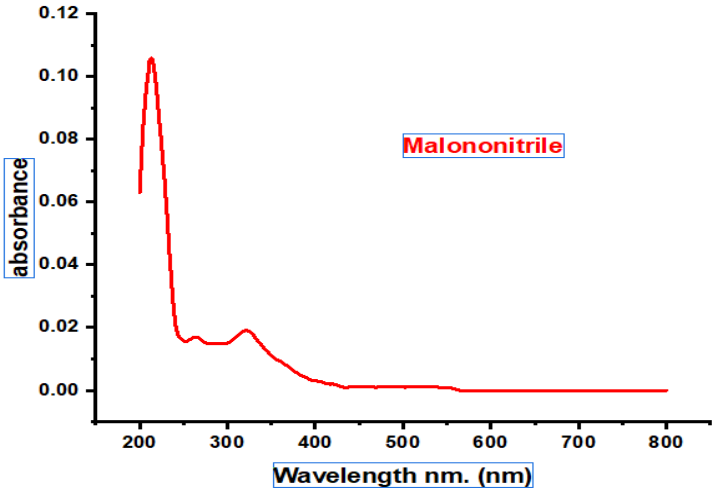


Figure 4.7 UV spectrum of Malononitrile in methanol

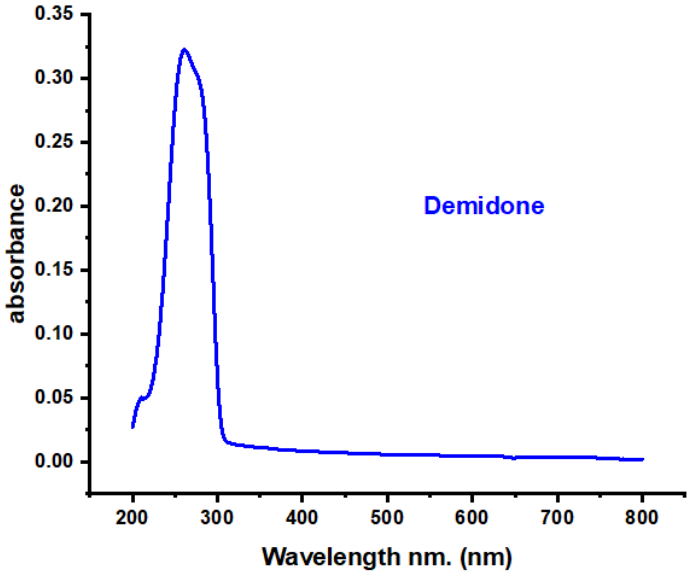


Figure 4.8 UV spectrum of Demidone in methanol

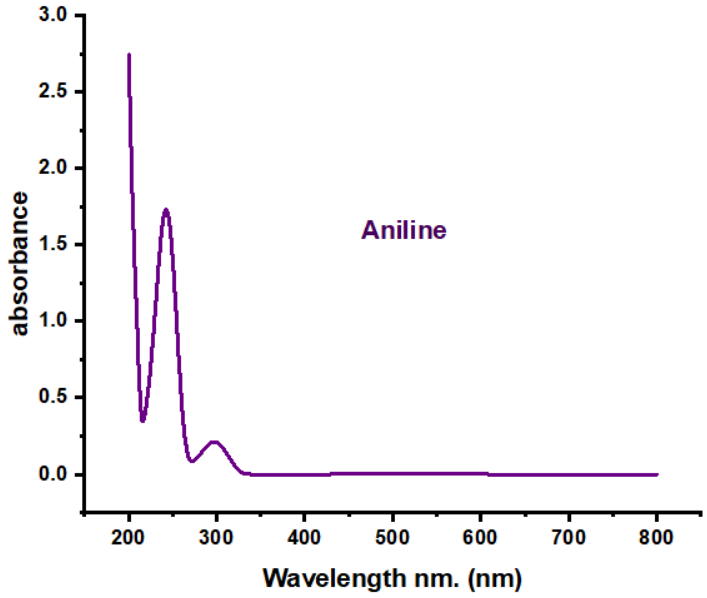


Figure 4.9 UV spectrum of Aniline in methanol

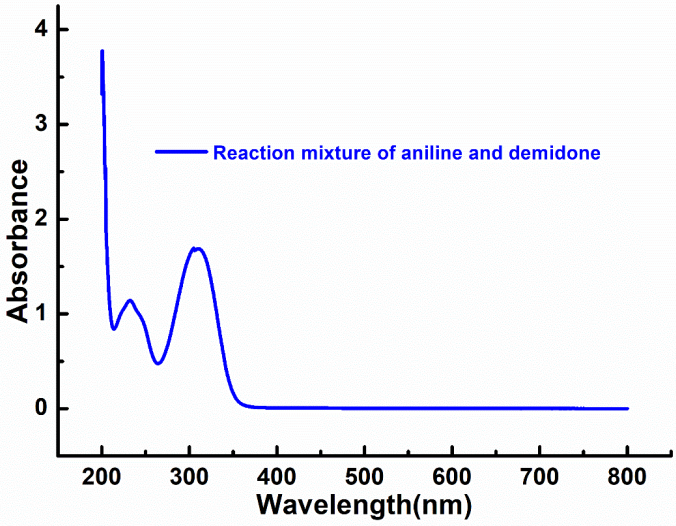


Figure 4.10 UV spectrum of reaction mixture of aniline and demidone in methanol

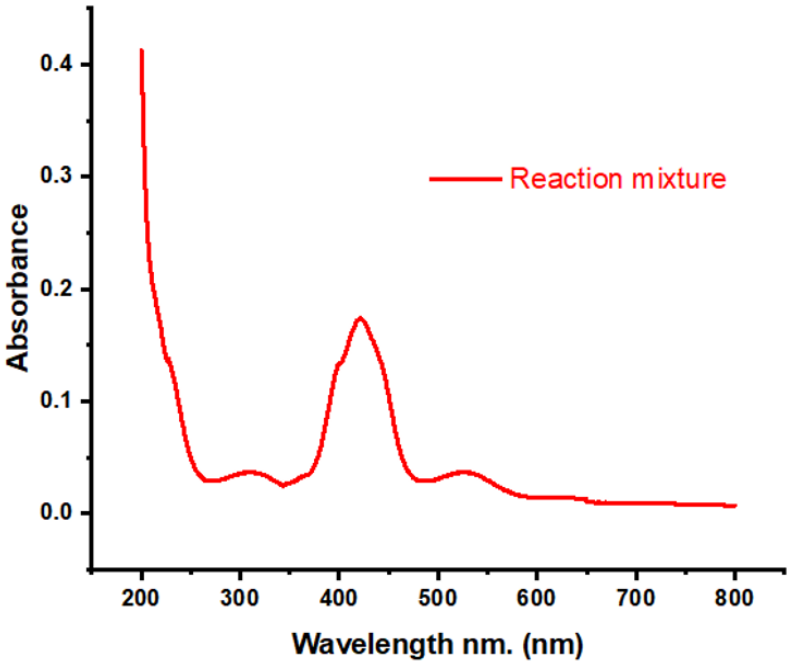
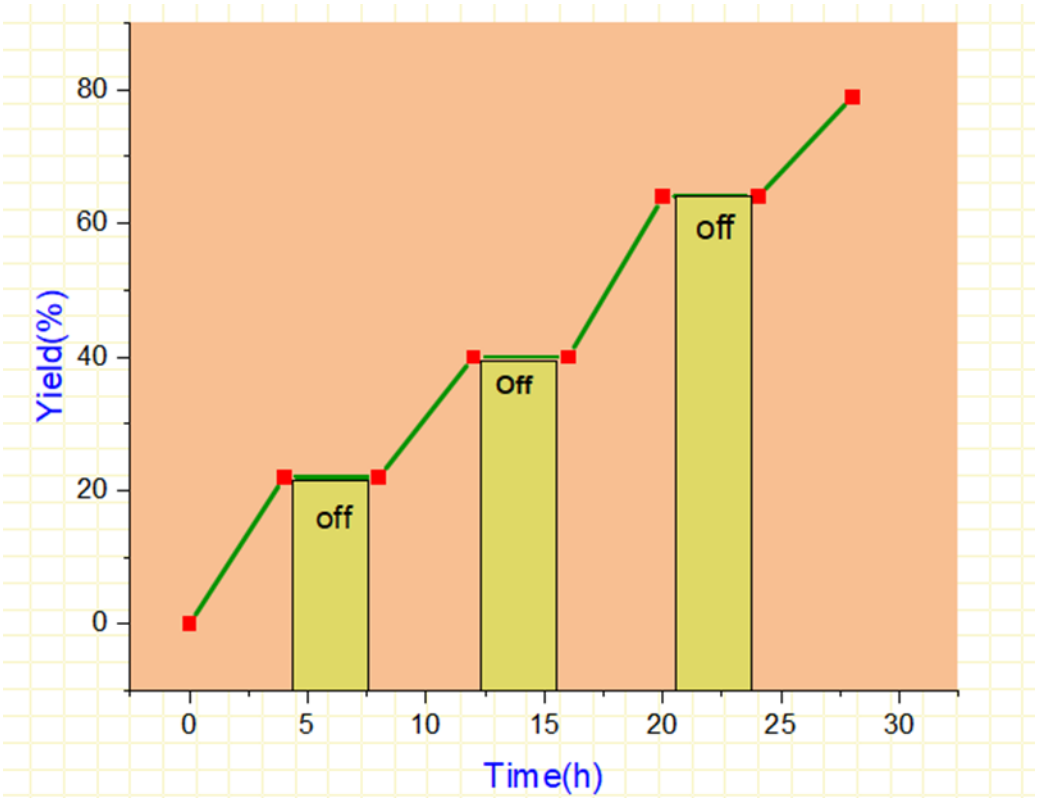


Figure 4.11 UV spectrum of reaction mixture in methanol

4.4.6. ON/OFF experiments

The reaction between Indole **1**, malononitrile **2**, and enaminone **3** was conducted under the standard conditions on a 0.25 mmol scale. The reaction mixture was subjected to sequential periods of stirring under visible light irradiation (22 W white LED) followed by stirring in the absence of light. At each time point, one reaction system was suspended, which was then purified with column chromatography on silica gel (Ethyl acetate: hexane) to give the corresponding products **4**. The yield of **4** was measured by weight of the product.



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