CHAPTER 4

Visible Light Assisted Synthesis of Dibarbiturates of Oxindole and Arylidene Barbituric Acid Derivatives Under Catalyst-free Condition

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4.1 Introduction

The exploitation of visible light, to induce important chemical transformations is a promising and sustainable approach in contemporary organic synthesis. The advantages of using visible light lie in the fact that it is a renewable, clean, abundant, inexpensive and environmentally friendly energy source for the execution of green chemical reactions [1-4]. In contrast to use of organic dyes as photocatalysts in organic transformations, numerous cases exist where organic transformations are carried out by visible light without any external photocatalyst. Hence, utilizing visible light in energy transfer processes for the sensitization of organic molecules to perform essential photochemical reactions would function as a valuable tool in green organic synthesis [5-9].

Barbituric acid derivatives play a very important role in pharmaceutical chemistry because they have various biological properties such as anticancer, antispasmodic, anxiolytics, sedative, anticonvulsant, hypnotic, and salt-forming reagents [10-15]. Barbituric acid has an "active" methylene group which is responsible for its condensation reactions with ketones or aldehydes lacking with α-hydrogen. The modification of biologically active indole moiety with biologically active barbiturate fragments would be helpful in designing medicinally significant compounds and recently anti-cancer activity of 5,5′-(2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)bis(1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione) system has been discovered **(Figure 4.1)** [16-19].

Arylidene barbituric acid derivatives are the significant class of sedative and hypnotic compounds. They have diverse laboratory and industrial applications, more significantly as intermediates in the preparation of heterocyclic compounds, oxadiazaflavines, benzyl barbituric derivatives, unsymmetrical disulphides, and as organic thermal stabilizers, medicinal antioxidants, and charge-generating agents. These compounds have also gained considerable attention due to their therapeutic applications such as inhibitors of methionine aminopeptidase-1 (MetAP-1), mushroom tyrosinase **(Figure 4.1)**, urease and many of them exhibit significant antifungal, antimicrobial, anticancer, and antitumor activities [20-28].

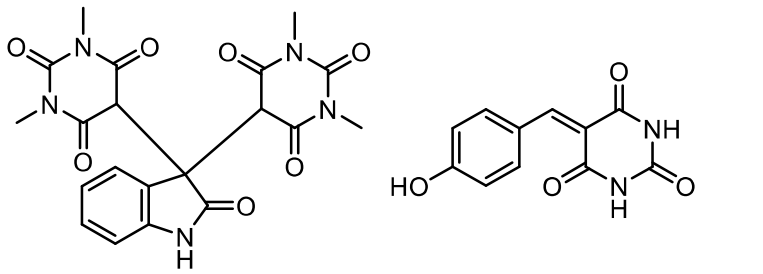
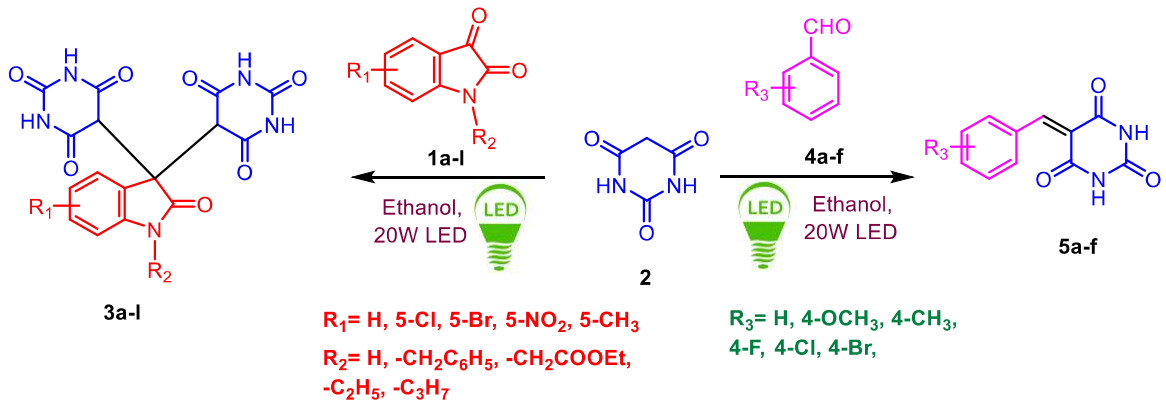


Figure 4.1 Biologically active dibarbiturate of oxindole and arylidene barbituric acid derivative.

Several approaches have been reported for the synthesis of dibarbiturates of oxindole such as under catalyst-free condition [29], by using catalysts like neutral alumina [30], oxalic acid dihydrate: proline mixture [31], by electrocatalytic method [32], and arylidene barbituric acid derivatives have been prepared by using catalysts such as sodium *p*-toluene sulfonate (NaPTSA) [33], Co_3O_4 nanoparticles [34], bentonite [35], ionic liquids 1-*n*-butyl-3-methylimmidazolium tetrafluoroborate ([bmim]BF_4) [36] and triphenyl(propyl-3-hydrogen sulfate)phosphonium bromide [37]. Still, they have many

limitations like use of toxic solvents, limited substrate scope, environmentally unfavourable conditions, expensive catalysts, longer reaction times, and operational difficulties. Thus, there is a demand of eco-friendly, high yielding, operationally simple, and green protocols using the high-atom economical pathway. In view of the above, we endeavour to highlight the recent advancement in visible light-mediated synthesis.

By considering all the above facts and as a part of our contemporary research on the design and construction of biologically active compounds [38-40], we herein reporting visible light-mediated, catalyst-free synthesis of dibarbiturates of oxindole and arylidene barbituric acid derivatives **(Scheme 4.1)**.



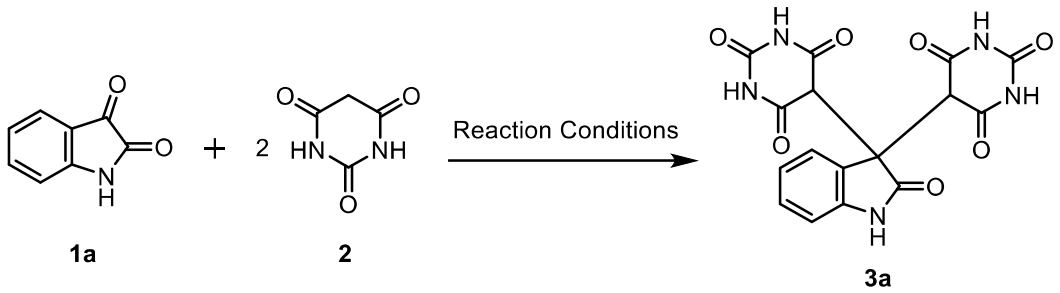
Scheme 4.1 Visible light-mediated, catalyst-free synthesis of dibarbiturates of oxindole **(3)** and arylidene barbituric acid derivatives **(5)**.

4.2 Results and Discussion

The work initiated by taking isatin (1.0 mmol), and barbituric acid (2.0 mmol) as a model reaction using 20 W white LED as a visible light source. The desired product **(3a)** was not obtained when 5 mol% of ZnO, TiO_2, and CuCl were used as catalysts and

ethanol as a solvent (**Table 4.1, entries 1-3**). When eosin Y, CH_3COOH and *p*-TSA (*p*-toluenesulfonic acid) were used, 10%, 12% and 18% of the product were obtained respectively (**Table 4.1, entries 3-6**). Surprisingly 95% of the product was obtained in 1h without any catalyst (**Table 4.1, entry 7**). Now different solvents were optimized under catalyst-free conditions. The desired product was not obtained when H_2O was used as a solvent while the ethanol: water (1:1) system gave 42% yield of the product (**Table 4.1, entries 8, 9**). Unfortunately, the product didn't form when THF (tetrahydrofuran), toluene, DMSO (dimethyl sulfoxide), and DMF (dimethylformamide) were used as solvents (**Table 4.1, entries 10-13**). Trace amount of product was isolated in the presence of DCM (dichloromethane) while ACN (acetonitrile) gave 35% of the product (**Table 4.1, entries 14, 15**). No product was obtained under solvent-free and catalyst-free conditions (**Table 4.1, entry 16**).

Table 4.1 Optimized reaction condition for the model reaction **3a**.[a]



1a + 2 **2** → **3a**

Entry	Catalyst (mol%)	Solvent (ml)	Time (h)	%Yield[b]
1	ZnO (5)	Ethanol (5)	10	N.R.
2	TiO_2 (5)	Ethanol (5)	12	N.R.

3	CuCl (5)	Ethanol (5)	6	N.R.
4	Eosin Y (5)	Ethanol (5)	8	10
5	CH_3COOH (5)	Ethanol (5)	7	12
6	*p*-TSA (5)	Ethanol (5)	9	18
7	**None**	**Ethanol (5)**	**1**	**95**
8	None	H_2O (5)	6	N.R.
9	None	Ethanol: H_2O (1:1) (5)	6	42
10	None	THF (5)	5	N.R.
11	None	Toluene (5)	5	N.R.
12	None	DMSO (5)	5	N.R.
13	None	DMF (5)	5	N.R.
14	None	DCM (5)	5	trace
15	None	ACN (5)	5	35
16	None	None	5	N.R.

[a]Reaction condition: isatin (1.0 mmol), barbituric acid (2.0 mmol), 20W white LED.
[b]Isolated yield.
N.R.= no reaction.

In order to discover the optimum reaction conditions, several parameters were explored. The reactions of isatin with barbituric acid, and benzaldehyde with barbituric acid were examined in detail by changing the molar proportions of the reactants (**Tables 4.2 and 4.3**). The perusal of **Tables 4.2** and **4.3** noticeably indicates that the best results were obtained using isatin, barbituric acid in the molar proportion 1.0: 2.0 (**Table 4.2,**

entry 2) and benzaldehyde, barbituric acid in the molar proportion 1.0: 1.0 (**Table 4.3, entry 1**) with 20 W white LED using ethanol as a solvent. One of the most interesting results from **Table 4.2** and **Table 4.3** was that two molecules of barbituric acid were attached with isatin (dibarbiturates) in any molar proportion while only one molecule of barbituric acid was attached with aldehyde (arylidene derivative).

Table 4.2 Effect of the molar ratio of substrates on the yield of the product **3a**.[a]

Entry	The molar ratio of reactants (isatin:barbituric acid)	%Yield[b]
1	1:1	46
2	**1:2**	**95**
3	2:1	48
4	1:3	84
5	1:4	71

[a]Reaction condition: isatin, barbituric acid, ethanol (5 ml), 20W white LED, 1h.
[b]Isolated yield.

Table 4.3 Effect of the molar ratio of substrates on the yield of the product **5a**.[a]

Entry	Molar ratio of reactants (benzaldehyde:barbituric acid)	%Yield[b]
1	**1:1**	**93**
2	1:2	90
3	2:1	43
4	1:3	80
5	1:4	69

[a]Reaction condition: benzaldehyde, barbituric acid, ethanol (5 ml), 20W white LED,1h.
[b]Isolated yield.

Further, the effect of time variation on the yield of the products **3a (Table 4.4)** and **5a (Table 4.5)** was also examined and it was observed that there was no significant change in the yield and type of the product with increase in time.

Table 4.4 Effect of time variation on the yield of the product **3a**.[a]

Entry	Time (h)	%Yield[b]
1	**1**	**95**
2	2	95
3	3	95
4	5	93

[a]Reaction condition: isatin (1.0 mmol), barbituric acid (2.0 mmol), 20W white LED, ethanol (5 ml).
[b]Isolated yield.

Table 4.5 Effect of time variation on the yield of the product **5a**.[a]

Entry	Time (h)	%Yield[b]
1	**1**	**93**
2	2	93
3	3	93
4	5	93

[a]Reaction condition: benzaldehyde (1.0 mmol), barbituric acid (1.0 mmol), 20W white LED, ethanol (5 ml).
[b]Isolated yield.

To find the optimal intensity of visible light, the reaction of isatin and barbituric acid was performed under visible light sources of different intensities (9W, 12W, 15W,

20W, and 30W) which is shown in **Table 4.6 and Figure 4.2**. The best result was observed with 20 W white LED (**Table 4.6, entry 4**). Nevertheless, at lower intensities of white LED, less yield of the product was observed in a long time (**Table 4.6, entries 1, 2, 3**). The use of higher intensity of white LED (30 W), in contrast, has no considerable effect on the yield of product or reaction time (**Table 4.6, entry 5**).

Table 4.6 Effect of the visible light intensity on the direction of the reaction **3a**.[a]

Entry	Visible light Intensity	Time (h)	Yield (%)[b]
1	9 W	6	56
2	12 W	7	62
3	15W	7	71
4	**20 W**	**1**	**95**
5	30 W	1	95

[a]Reaction condition: isatin (1.0 mmol), barbituric acid (2.0 mmol), ethanol (5 ml).
[b]Isolated yield.

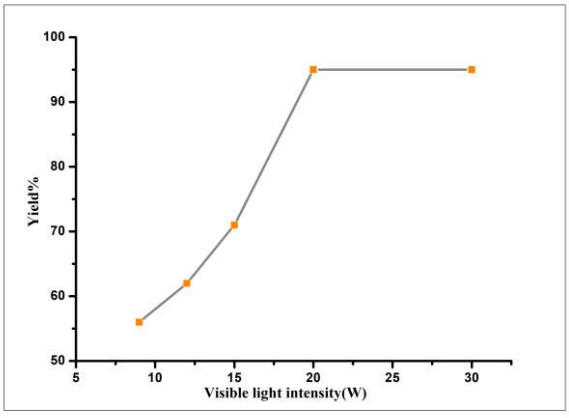
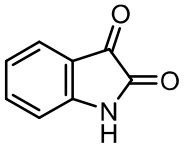
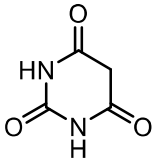
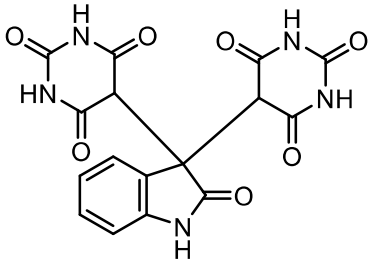
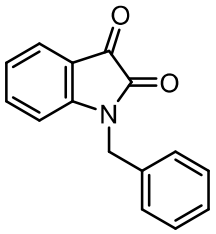
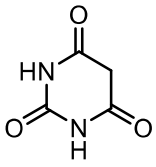
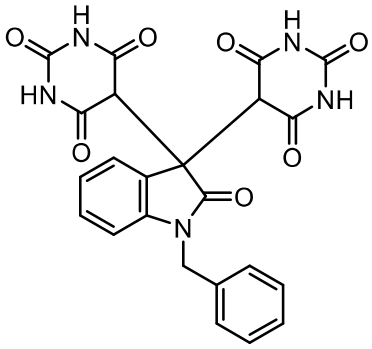
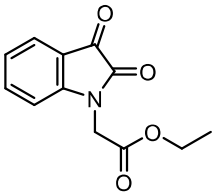
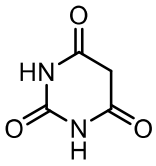
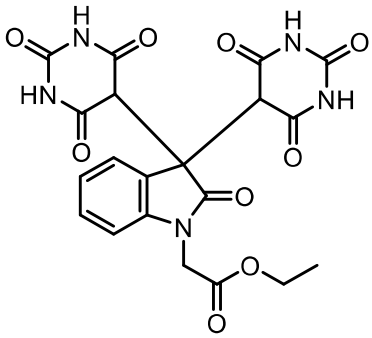
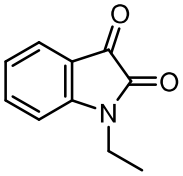
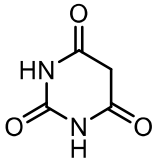
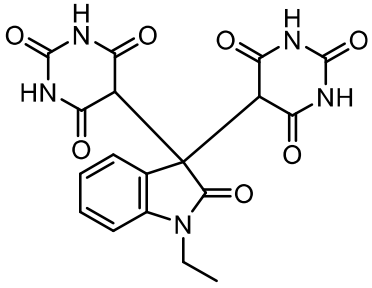
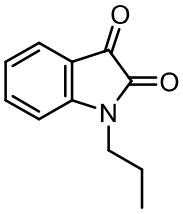
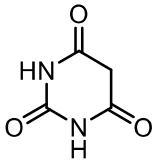
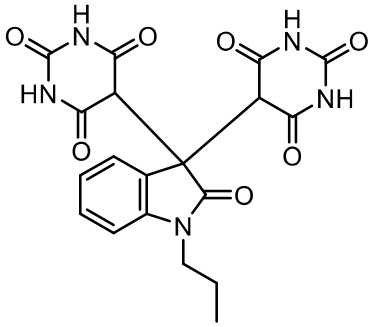


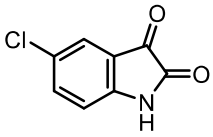
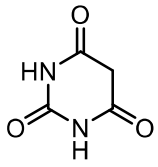
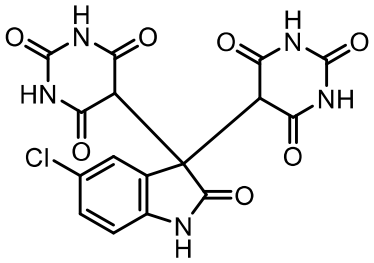
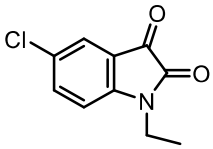
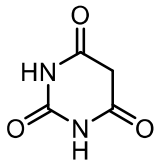
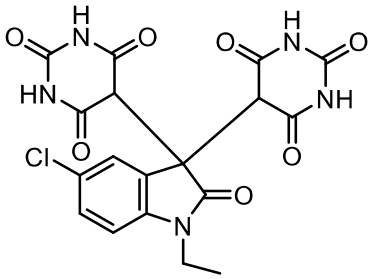
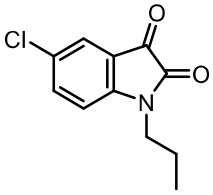
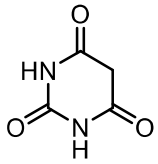
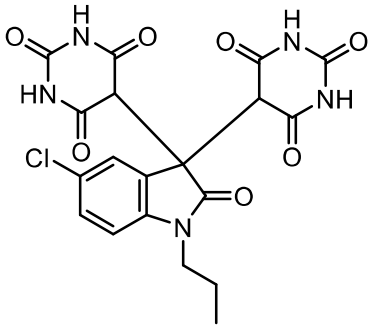
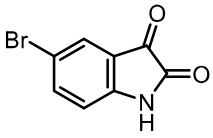
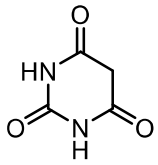
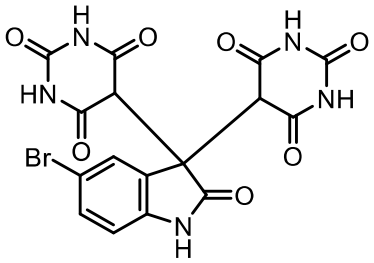
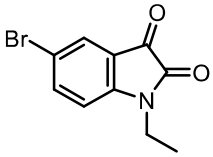
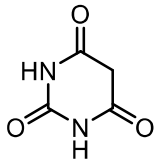
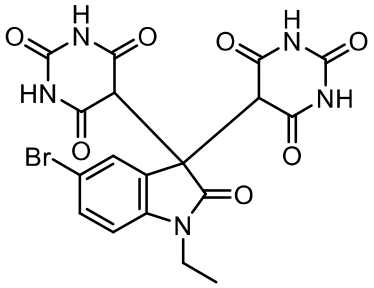
Figure 4.2 Yield (%) vs visible light intensity for the synthesis of 5,5′-(2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**3a**)

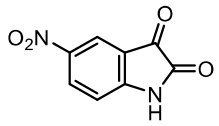
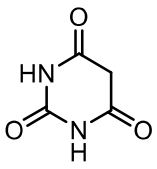
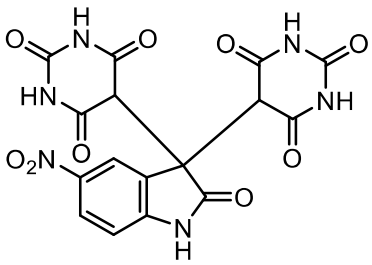
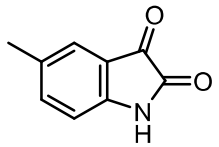
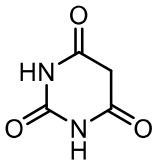
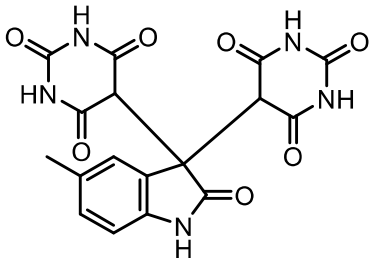
A wide range of substituted isatin such as isatin **(1a)**, 1-benzylisatin **(1b)**, ethyl 2-(2,3-dioxoindolin-1-yl)acetate **(1c)**, 1-ethylisatin **(1d)**, 1-propylisatin **(1e)**, 5-chloroisatin **(1f)**, 5-chloro-1-ethylisatin **(1g)**, 5-chloro-1-propylisatin **(1h)**, 5-bromoisatin **(1i)**, 5-bromo-1-ethylisatin **(1j)**, 5-nitroisatin **(1k)**, 5-methylisatin **(1l)** and aryl aldehydes like benzaldehyde **(4a)**, 4-methylbenzaldehyde **(4b)**, 4-methoxybenzaldehyde **(4c)**, 4-fluorobenzaldehyde **(4d)**, 4-chlorobenzaldehyde **(4e)**, 4-bromobenzaldehyde **(4f)**, i.e., both electron-donating as well as electron-withdrawing groups, were investigated under the optimal conditions to extend the scope of this methodology. They worked proficiently with barbituric acid to afford the products in excellent yields (90-95%) (**Table 4.7** and **4.8**).

Table 4.7 Screening of substrates for the synthesis of dibarbiturates of oxindole. [a]

Entry	1	2	3[a]	Yield[b] (%)
3a	 1a			95

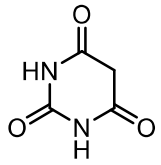
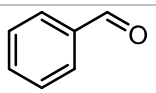
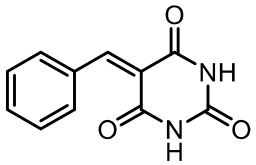
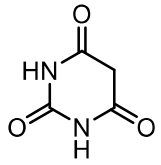
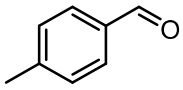
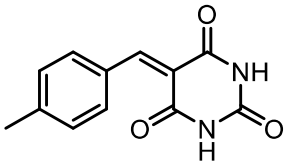
3b	 **1b**			**93**
3c	 **1c**			**94**
3d	 **1d**			**91**
3e	 **1e**			**90**

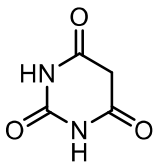
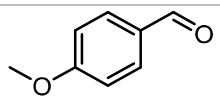
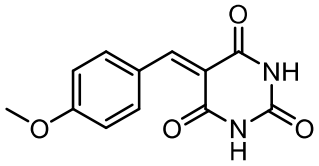
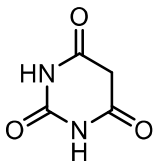
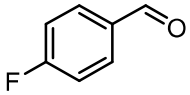
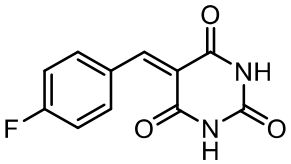
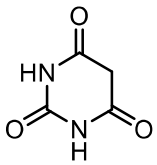
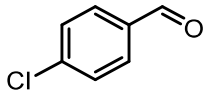
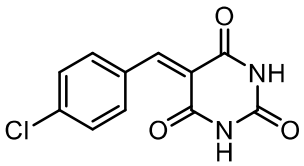
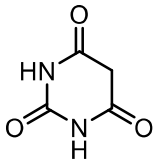
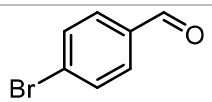
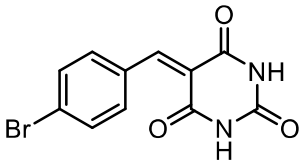
3f	 **1f**			**92**
3g	 **1g**			**95**
3h	 **1h**			**90**
3i	 **1i**			**92**
3j	 **1j**			**94**

3k	 **1k**			**91**
3l	 **1l**			**90**

[a] Products were characterized by ^{1}H, ^{13}C NMR and IR spectroscopy.
[b] Isolated yield.

Table 4.8 Screening of substrates for the synthesis of arylidene barbituric acid derivatives. [a]

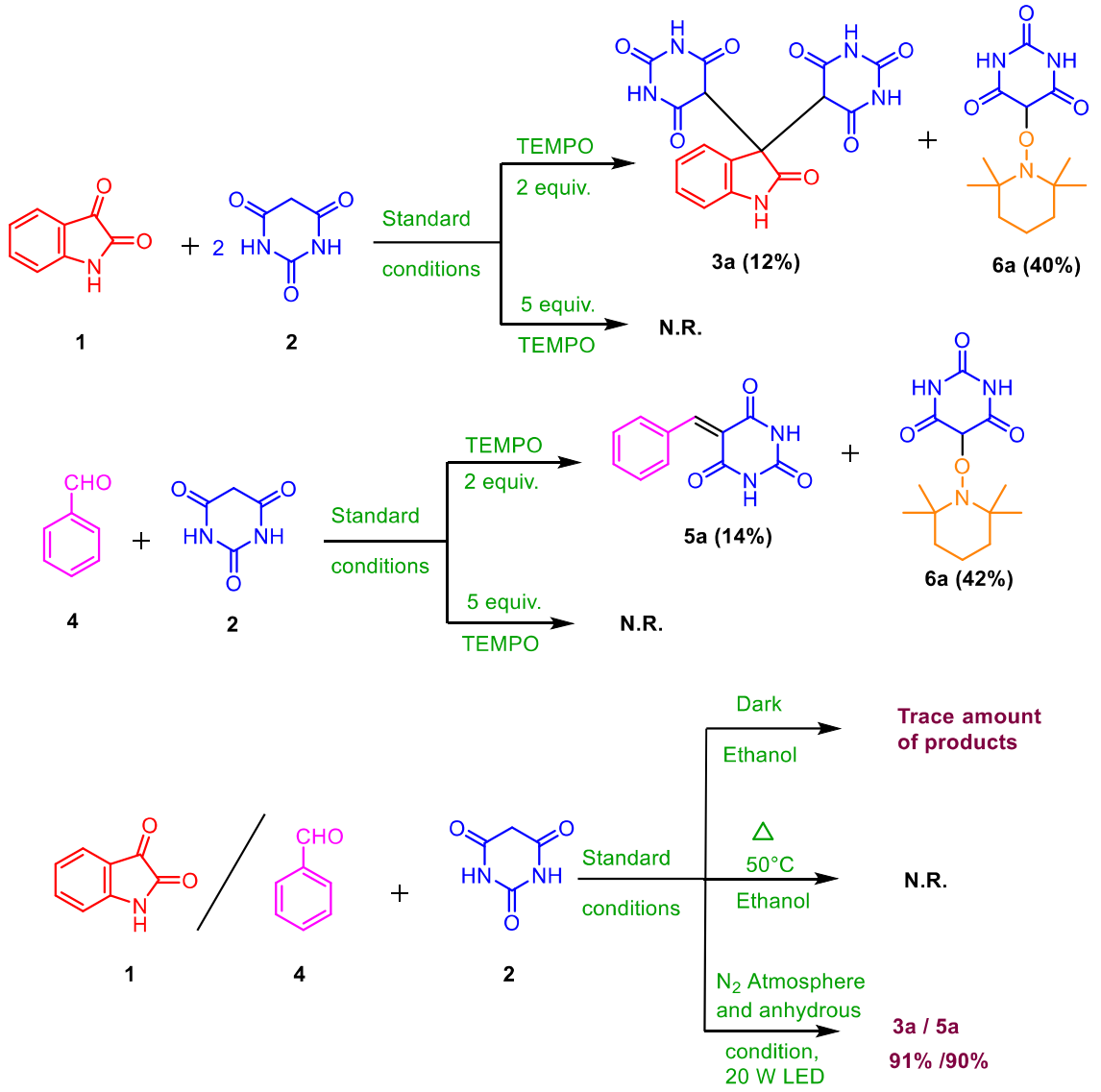
Entry	**2**	**4**	**5**[a]	**Yield**[b] **(%)**
5a		 **4a**		**93**
5b		 **4b**		**95**

5c		 **4c**		**91**
5d		 **4d**		**94**
5e		 **4e**		**91**
5f		 **4f**		**92**

[a] Products were characterized by ^{1}H, ^{13}C NMR and IR spectroscopy.
[b] Isolated yield.

Some control experiments were conducted to establish the reaction mechanism. By carrying out a quenching experiment with a radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl, it was established that, there was participation of free-radical species in the reaction. The model reactions gave the corresponding products **3a** and **5a** in 12% and 14% yields respectively in the presence of 2 equiv. of TEMPO, under standard conditions. The involvement of a free radical in the mechanism was further confirmed by the formation of adduct 5-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **(6a)** which was characterized by the ^{1}H and ^{13}C NMR spectroscopy. However, the product formation quenched entirely with 5

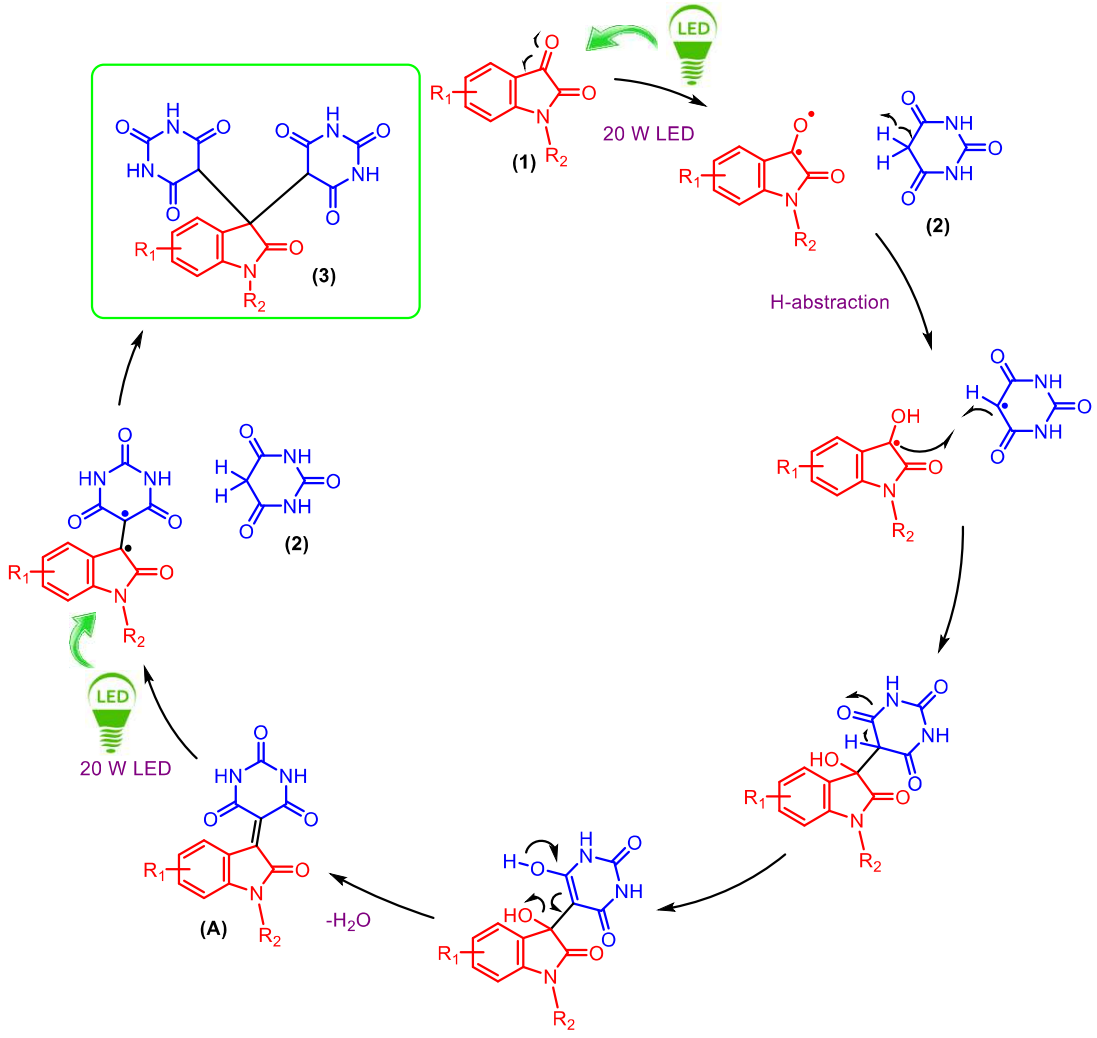
equivalents of TEMPO. Thus, the participation of radical intermediate was recognized by the inhibitory action of TEMPO **(Scheme 4.2)**. There was a formation of a trace amount of product in the absence of visible light, i.e. in dark condition at room temperature, and when the same reaction was carried out at 50°C, there was no product formation.



Scheme 4.2 Control experiments to establish mechanism of the reaction.

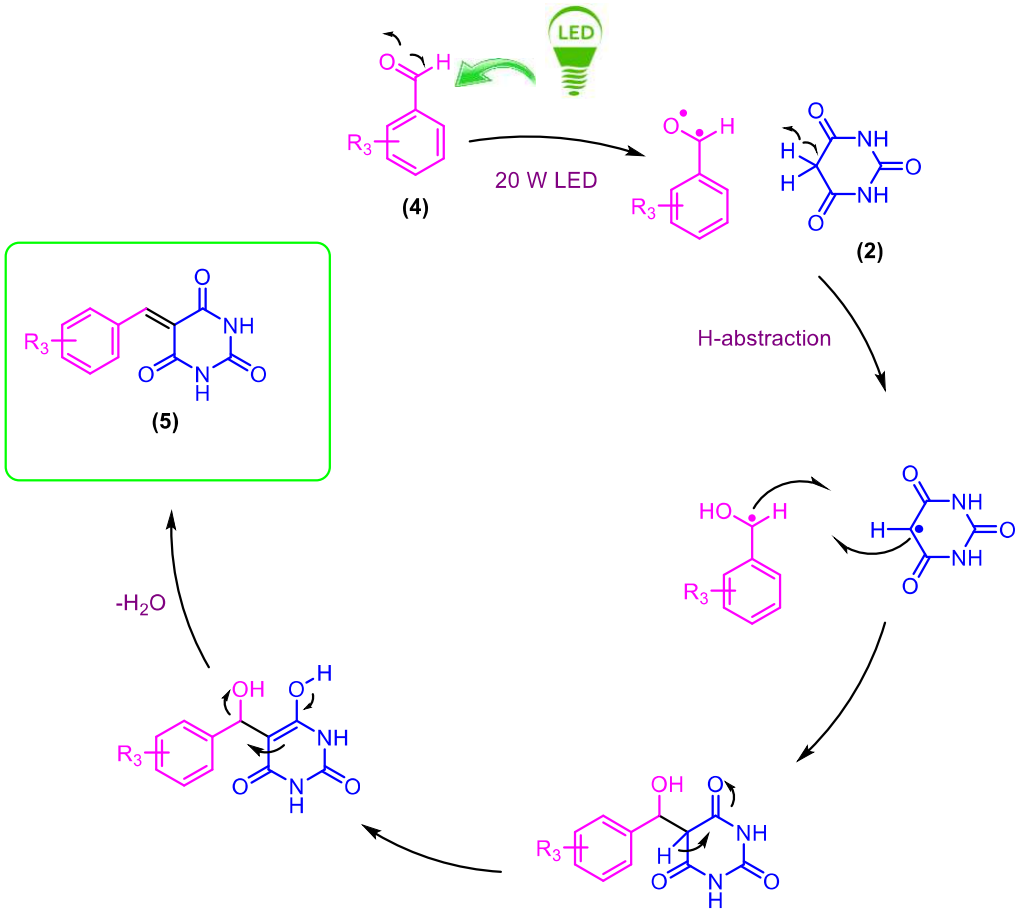
These two results reveal the importance of visible light for this reaction. There was a minor decrease in the yield (91% / 90%) of the product **(Scheme 4.2)** when the reaction was carried out under anhydrous condition and inert atmosphere (in the presence of N_2 gas). These results indicate that there is no role of oxygen or water in carrying out the reaction.

The plausible reaction mechanism for the formation of dibarbiturates of oxindole **(3)** and arylidene barbituric acid derivatives **(5)** are given in **Schemes 4.3 and 4.4** based



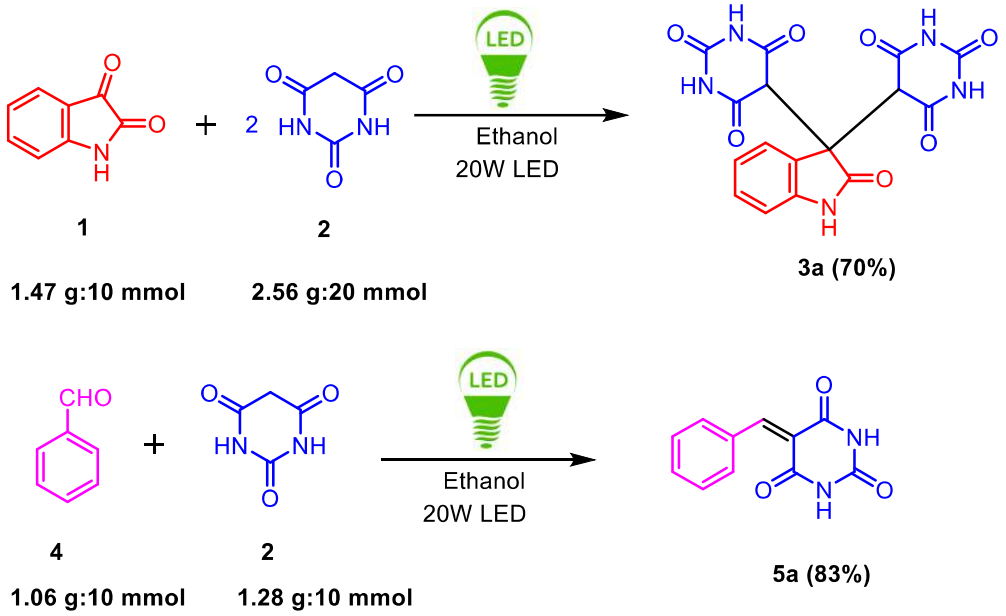
Scheme 4.3 Plausible reaction mechanism for dibarbiturates of oxindole **(3)**.

on the isolated product, reported literature, UV spectra, and controlled experiments. Initially, the formation of free radical of isatin **(1)** takes place by the irradiation of visible light. This free radical abstracts hydrogen radical from barbituric acid **(2),** and formation of **(A)** occurs after removal of H_2O. This intermediate **(A)** forms free radical after irradiation and reacts in the previous way to produce the desired product **(3)**. In **Scheme 4.4,** aryl aldehyde **(4)** forms the free radical and abstracts hydrogen radical from barbituric acid **(2),** which leads to the formation of product **(5)** after removal of H_2O.



Scheme 4.4 Plausible reaction mechanism for arylidene barbituric acid derivatives **(5)**.

4.2.1 Gram-Scale Synthesis of Dibarbiturates of Oxindole and Arylidene Barbituric Acid Derivatives



Scheme 4.5 Gram-scale synthesis of dibarbiturates of oxindole **(3a)** and arylidene barbituric acid derivatives **(5a)** under visible light condition.

Furthermore, the practicality was authenticated by performing the model reaction in gram-scale **(Scheme 4.5)**. Isatin **1** (10.0 mmol) with barbituric acid **2** (20.0 mmol) or benzaldehyde **4** (10.0 mmol) with barbituric acid **2** (10.0 mmol) were stirred at room temperature under irradiation of 20 W white LED by using ethanol (50 ml) as a solvent. After the completion of reaction, the reaction mixture was filtered to obtain the solid product. Then, crude product was recrystallized from ethanol to afford the pure product (**3a, 70%** and **5a, 83%** respectively).

4.3 Conclusion

In summary, we have developed a practical and resourceful protocol for the synthesis of biologically active dibarbiturates of oxindole and arylidene barbituric acid derivatives by the condensation of carbonyl compounds with barbituric acid under catalyst-free condition. The exploitation of visible light as a green, inexpensive, and environmentally friendly energy source is a significant feature of this protocol. Products are obtained in high yields without any chromatographic purification by using readily available starting materials.

4.4 Experimental Section

4.4.1 General Experimental Procedure for Synthesis of Dibarbiturates of Oxindole and Arylidene Barbituric Acid Derivatives (3a-l and 5a-f)

Isatin **1** (1.0 mmol) with barbituric acid **2** (2.0 mmol) or aryl aldehyde **4** (1.0 mmol) with barbituric acid **2** (1.0 mmol) were stirred at room temperature under irradiation of 20 W white LED by using ethanol (5 ml) as a solvent. After the completion of reaction (monitored by TLC), the solid product was filtered and the crude product was recrystallized from ethanol to afford the pure product (**3** and **5** respectively).

4.4.2 Analytical Data

5,5′-(2-Oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3a) White solid (95% yield); mp:285-290^{o}C (dec); **IR (KBr)** ν cm^{-1}: 3330, 3234, 3152, 3065, 1725, 1663, 1645; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.18 (s, 4H,NH),

10.56 (s, 1H,NH), 7.16-7.12 (m, 2H, Ar-H), 6.91-6.88 (m, 1H, Ar-H), 6.69 (d, 1H, Ar-H), 5.05 (s, 2H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 176.13, 168.22, 150.69, 143.65, 129.26, 128.56, 124.74, 121.92, 109.92, 53.95, 51.23; **Anal. Calc. for $C_{16}H_{11}N_5O_7$:** C, 49.88; H, 2.88; N, 18.18; Found: C, 49.75; H, 2.62; N, 18.35.

5,5′-(1-Benzyl-2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3b) White solid (93% yield); mp:238-242^{o}C (dec); **IR (KBr)** *ν* cm^{-1}: 3352, 3246, 3126, 3042, 1716, 1673, 1645; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 11.29 (s, 4H,NH), 7.34-7.31 (m, 4H, Ar-H), 7.28 (d, 1H, Ar-H), 7.22 (d, 1H, Ar-H), 7.15 (t, 1H, Ar-H), 6.98 (t, 1H, Ar-H), 6.61 (d, 1H, Ar-H), 5.23 (s, 2H,CH), 4.77 (s, 2H,CH_2). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 174.98, 168.28, 150.67, 144.20, 136.32, 129.32, 129.07, 128.01, 127.55, 124.59, 122.78, 109.60, 56.50, 53.36, 44.20; **Anal. Calc. for $C_{23}H_{17}N_5O_7$:** C, 58.11; H, 3.60; N, 14.73; Found: C, 58.35; H, 3.42; N, 14.61.

5,5′-(1-(2-Ethoxy-2-oxoethyl)-2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3c) White solid (94% yield); mp:217-220^{o}C; **IR (KBr)** *ν* cm^{-1}: 3342, 3266, 3156, 3062,1735, 1720, 1663, 1643; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 11.21 (s, 4H,NH), 7.24 (t, 1H, Ar-H), 7.20 (d, 1H, Ar-H), 7.00 (t, 1H, Ar-H), 6.91 (d, 1H, Ar-H), 5.17 (s, 2H,CH), 4.36 (s, 2H,CH_2), 4.16-4.12 (m, 2H,CH_2), 1.19 (t, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 174.57, 168.27, 167.59, 150.61, 143.76, 129.33, 127.49, 124.73, 122.83, 109.40, 61.41, 56.40, 53.14, 42.37, 14.51; **Anal. Calc. for $C_{20}H_{17}N_5O_9$:** C, 50.96; H, 3.64; N, 14.86; Found: C, 50.85; H, 3.87; N, 14.63.

5,5′-(1-Ethyl-2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3d) White solid (91% yield); mp:230-235°C (dec); **IR (KBr)** *ν* cm^{-1}: 3328, 3296, 3176, 3049, 1710, 1659, 1641; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.22 (s, 3H,NH), 11.14 (s, 1H,NH), 7.25 (t, 1H, Ar-H), 7.19 (d, 1H, Ar-H), 6.99 - 6.92 (m, 2H, Ar-H), 5.08 (s, 2H,CH), 3.64 - 3.58 (m, 2H,CH_2), 1.11 (t, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 174.04, 168.27, 150.72, 144.05, 129.42, 128.01, 124.59, 122.45, 108.88, 53.04, 51.42, 34.70, 12.10; **Anal. Calc. for $C_{18}H_{15}N_5O_7$:** C, 52.30; H, 3.66; N, 16.94; Found: C, 52.41; H, 3.75; N, 16.72.

5,5′-(2-Oxo-1-propyl-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3e) White solid (90% yield); mp:200-204°C (dec); **IR (KBr)** *ν* cm^{-1}: 3351, 3290, 3163, 3044, 1715, 1682, 1635; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.22 (s, 4H,NH), 7.23 (d, 1H, Ar-H), 7.18 (d, 1H, Ar-H), 7.00 - 6.88 (m, 2H, Ar-H), 5.09 (s, 2H,CH), 3.63-3.60 (t, 2H,CH_2), 1.57-1.53 (m, 2H,CH_2), 0.89 (t, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 174.39, 168.27, 150.69, 144.67, 129.42, 127.88, 124.49, 122.42, 109.03, 53.10, 51.25, 41.86, 20.46, 11.85; **Anal. Calc. for $C_{19}H_{17}N_5O_7$:** C, 53.40; H, 4.01; N, 16.39; Found: C, 53.21; H, 4.23; N, 16.52.

5,5′-(5-Chloro-2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3f) White solid (92% yield); mp:232-236°C (dec); **IR (KBr)** *ν* cm^{-1}: 3346, 3270, 3183, 3034, 1716, 1690, 1638; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.26 (s, 4H,NH), 10.74 (s, 1H,NH), 7.22 (d, 1H, Ar-H), 7.15 (s, 1H, Ar-H), 6.72 (d, 1H, Ar-H), 5.05 (s, 2H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 176.07,

168.22, 150.69, 142.85, 130.84, 129.11, 125.64, 125.12, 111.21, 56.50, 53.46; **Anal. Calc. for $C_{16}H_{10}ClN_5O_7$:** C, 45.79; H, 2.40; N, 16.69; Found: C, 45.63; H, 2.23; N, 16.57.

5,5′-(5-Chloro-1-ethyl-2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3g) White solid (95% yield); mp:258-260°C (dec); **IR (KBr)** *v* cm^{-1}: 3360, 3286, 3153, 3042, 1711, 1676, 1650; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)**= 11.29 (s, 4H,NH), 7.33 (d, 1H, Ar-H), 7.20 (s, 1H, Ar-H), 7.00 (d, 1H, Ar-H), 5.08 (s, 2H,CH), 3.70-3.59 (m, 2H,CH_2), 1.09 (t, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)**= 173.94, 168.27, 150.76, 143.26, 130.18, 129.21, 126.22, 125.05, 110.27, 56.50, 52.53, 34.89, 11.98; **Anal. Calc. for $C_{18}H_{14}ClN_5O_7$:** C, 48.28; H, 3.15; N, 15.64; Found: C, 48.46; H, 3.23; N, 15.49.

5,5′-(5-Chloro-2-oxo-1-propyl-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3h) White solid (90% yield); mp:246-250°C (dec); **IR (KBr)** *v* cm^{-1}: 3350, 3281, 3145, 3058, 1725, 1659, 1629; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)**= 11.28 (s, 4H,NH), 7.32 (d, 1H, Ar-H), 7.19 (s, 1H, Ar-H), 7.01 (d, 1H, Ar-H), 5.09 (s, 2H,CH), 3.63-3.60 (t, 2H,CH_2), 1.56-1.52 (m, 2H,CH_2), 0.89 (t, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)**= 174.29, 168.28, 150.75, 143.90, 130.09, 129.17, 126.17, 124.96, 110.43, 56.50, 52.56, 41.98, 20.40, 11.79; **Anal. Calc. for $C_{19}H_{16}ClN_5O_7$:** C, 49.42; H, 3.49; N, 15.17; Found: C, 49.68; H, 3.63; N, 15.39.

5,5′-(5-Bromo-2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3i) White solid (92% yield); mp: 260-265°C; **IR (KBr)** *v* cm^{-1}: 3340, 3285, 3171, 3055, 1705, 1673, 1650; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)**=

11.28 (s, 4H,NH), 10.76 (s, 1H,NH), 7.35 - 7.26 (m, 2H, Ar-H), 6.68 (s, 1H, Ar-H), 5.04 (s, 2H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 175.98, 168.26, 150.73, 143.22, 131.96, 131.24, 127.76, 113.42, 111.76, 56.50, 53.36; **Anal. Calc. for $C_{16}H_{10}BrN_5O_7$:** C, 41.40; H, 2.17; N, 15.09; Found: C, 41.57; H, 2.33; N, 15.21.

5,5′-(5-Bromo-1-ethyl-2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3j) White solid (94% yield); mp:250-252°C (dec); **IR (KBr)** *ν* cm^{-1}: 3357, 3277, 3169, 3060, 1710, 1681, 1643; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.30 (s, 3H,NH), 11.15 (s, 1H,NH), 7.33 (d, 1H, Ar-H), 7.19 (s, 1H, Ar-H), 7.00 (d, 1H, Ar-H), 5.08 (s, 2H,CH), 3.61-3.46 (m, 2H,CH_2), 1.09 (t, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 173.62, 167.96, 150.43, 142.93, 129.84, 128.91, 125.90, 124.72, 109.96, 56.19, 52.21, 34.58, 11.66; **Anal. Calc. for $C_{18}H_{14}BrN_5O_7$:** C, 43.92; H, 2.87; N, 14.23; Found: C, 43.78; H, 2.63; N, 14.49.

5,5′-(5-Nitro-2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3k) White solid (91% yield); mp:200-205°C (dec); **IR (KBr)** *ν* cm^{-1}: 3361, 3287, 3159, 3040, 1718, 1686, 1655; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.39 (s, 4H,NH), 11.35 (s, 1H,NH), 8.17 - 8.08 (m, 2H, Ar-H), 6.92 (d, 1H, Ar-H), 5.15 (s, 2H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 176.97, 168.28, 150.73, 150.45, 142.32, 129.88, 126.61, 121.35, 109.89, 56.28, 52.77; **Anal. Calc. for $C_{16}H_{10}N_6O_9$:** C, 44.66; H, 2.34; N, 19.53; Found: C, 44.58; H, 2.53; N, 19.69.

5,5′-(5-Methyl-2-oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3l) White solid (90% yield); mp:212-215°C (dec); **IR (KBr)** *ν*

cm^{-1}: 3371, 3290, 3166, 3046, 1714, 1678, 1640; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 11.21 (s, 4H,NH), 10.48 (s, 1H,NH), 6.96 (d, 2H, Ar-H), 6.59 (d, 1H, Ar-H), 5.00 (s, 2H,CH), 2.20 (s, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 176.14, 168.29, 150.74, 141.26, 130.47, 129.60, 128.62, 125.33, 109.68, 53.93, 51.31, 39.64, 39.47, 39.30, 21.41; **Anal. Calc. for $C_{17}H_{13}N_5O_7$:** C, 51.13; H, 3.28; N, 17.54; Found: C, 51.28; H, 3.43; N, 17.39.

5-Benzylidenebarbituric acid (5a) White solid (93% yield); mp:265-270^{o}C; **IR (KBr)** *v* cm^{-1}: 3240, 3075, 1758, 1710, 1676, 1568; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 11.40 (s, 1H,NH), 11.24 (s, 1H,NH), 8.29 (s, 1H,CH), 8.08 (d, 2H, Ar-H), 7.55 - 7.52 (m, 1H, Ar-H), 7.49 - 7.46 (m, 2H, Ar-H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.86, 162.04, 155.17, 150.67, 133.56, 133.14, 132.67, 128.51, 119.57; **Anal. Calc. for $C_{11}H_8N_2O_3$:** C, 61.11; H, 3.73; N, 12.96; Found: C, 61.37; H, 3.58; N, 12.67.

5-(4-Methylbenzylidene)barbituric acid (5b) White solid (95% yield); mp:280-282^{o}C; **IR (KBr)** *v* cm^{-1}: 3228, 3071, 1748, 1714, 1660, 1545; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 11.36 (s, 1H,NH), 11.21 (s, 1H,NH), 8.24 (s, 1H,CH), 8.07 (d, 2H, Ar-H), 7.27 (d, 2H, Ar-H), 2.36 (s, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 164.04, 162.21, 155.57, 150.65, 143.96, 134.47, 130.28, 129.29, 118.16, 21.81; **Anal. Calc. for $C_{12}H_{10}N_2O_3$:** C, 62.61; H, 4.38; N, 12.17; Found: C, 62.87; H, 4.53; N, 12.39.

5-(4-Methoxybenzylidene)barbituric acid (5c) Yellow solid (91% yield); mp>300^{o}C; **IR (KBr)** *v* cm^{-1}: 3202, 3090, 1708, 1681, 1647, 1592, 1425; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 11.31 (s, 1H,NH), 11.18 (s, 1H,NH), 8.35 (d, 2H, Ar-H), 8.24 (s,

1H,CH), 7.05 (d, 2H, Ar-H), 3.86 (s, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 164.39, 163.91, 162.63, 155.47, 150.68, 137.96, 125.59, 115.92, 114.39, 56.14; **Anal. Calc. for $C_{12}H_{10}N_2O_4$:** C, 58.54; H, 4.09; N, 11.38; Found: C, 58.77; H, 4.23; N, 11.56.

5-(4-Fluorobenzylidene)barbituric acid (5d) White solid (94% yield); mp:260-262°C; **IR (KBr)** *v* cm^{-1}: 3230, 3072, 1755, 1710, 1661, 1558; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 11.42 (s, 1H,NH), 11.27 (s, 1H,NH), 8.26 (s, 1H,CH), 8.24 - 8.21 (m, 2H, Ar-H), 7.31 (t, 2H, Ar-H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.87, 162.20, 153.94, 150.67, 136.85, 136.78, 129.65, 119.12, 115.76; **Anal. Calc. for $C_{11}H_7FN_2O_3$:** C, 56.42; H, 3.01; N, 11.96; Found: C, 56.61; H, 3.23; N, 11.74.

5-(4-Chlorobenzylidene)barbituric acid (5e) White solid (91% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3224, 3085, 1756, 1704, 1670, 1562; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 11.43 (s, 1H,NH), 11.28 (s, 1H,NH), 8.22 (s, 1H,CH), 7.97 (d, 2H, Ar-H), 7.66 (d, 2H, Ar-H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.67, 162.04, 153.58, 150.66, 135.15, 132.77, 132.38, 131.72, 131.50, 126.31, 120.21; **Anal. Calc. for $C_{11}H_7ClN_2O_3$:** C, 52.71; H, 2.82; N, 11.18; Found: C, 52.87; H, 2.63; N, 11.37.

5-(4-Bromobenzylidene)barbituric acid (5f) White solid (92% yield); mp:286-288°C; **IR (KBr)** *v* cm^{-1}: 3234, 3065, 1752, 1710, 1665, 1560; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 11.43 (s, 1H,NH), 11.28 (s, 1H,NH), 8.24 (s, 1H,CH), 8.06 (d, 2H, Ar-H), 7.52 (d, 2H, Ar-H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.69, 162.05, 153.51,

150.66, 137.21, 135.14, 132.01, 129.83, 128.55, 120.10; **Anal. Calc. for $C_{11}H_7BrN_2O_3$:** C, 44.77; H, 2.39; N, 9.49; Found: C, 44.51; H, 2.53; N, 9.64.

5-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6a) **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.07 (s, 1H,NH), 10.83 (s, 1H,NH), 3.44 (s, 1H,CH), 1.67 - 1.53 (m, 6H,CH_2), 1.32 (s, 6H,CH_3), 1.11 (s, 6H,CH_3). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 173.31, 152.15, 82.32, 56.36, 34.88, 27.43, 16.25.

4.4.3 Spectral Data of Product 5,5′-(2-Oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3a)

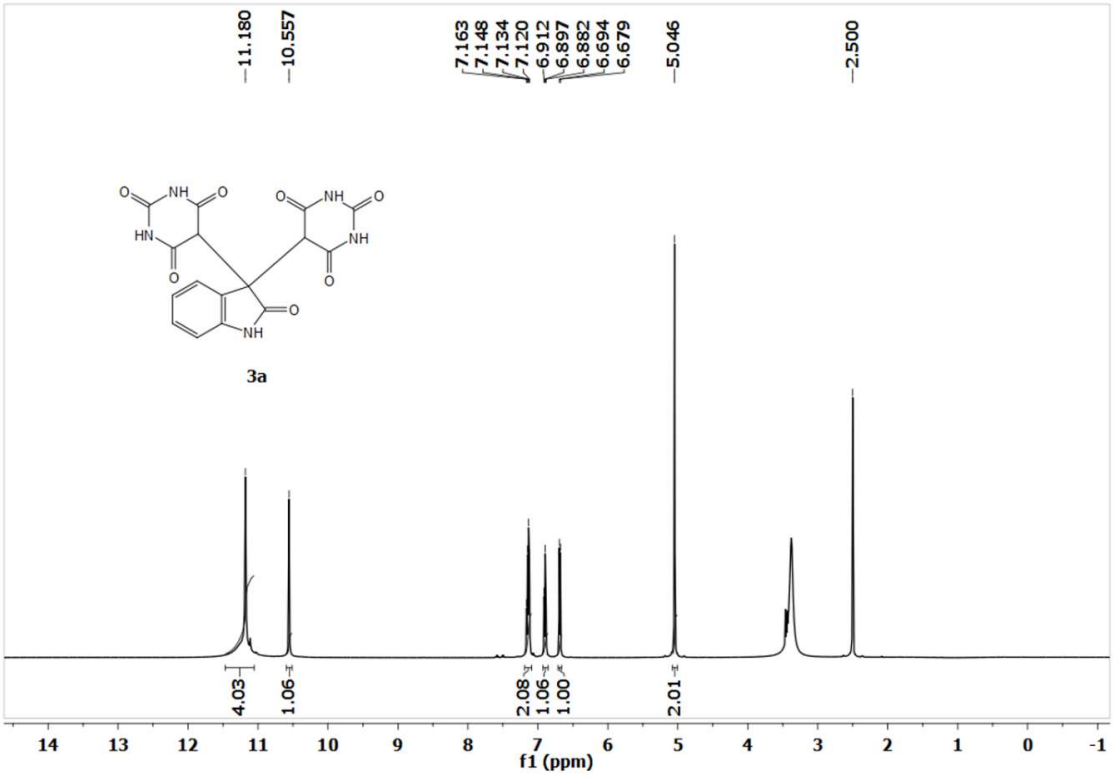


Figure 4.3 ^{1}H NMR of 5,5′-(2-Oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3a)

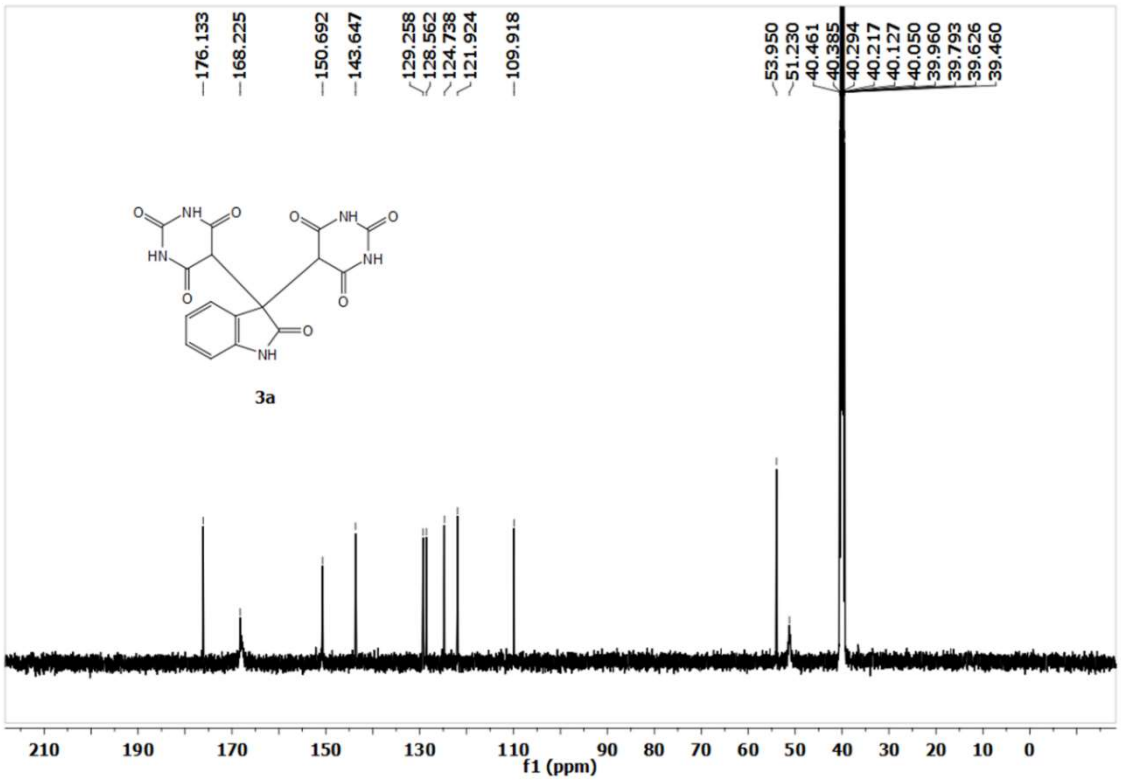


Figure 4.4 ^{13}C NMR of 5,5′-(2-Oxo-2,3-dihydro-1*H*-indole-3,3-diyl)dipyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3a)

4.4.4 Spectral Data of Product 5-Benzylidenebarbituric acid (5a)

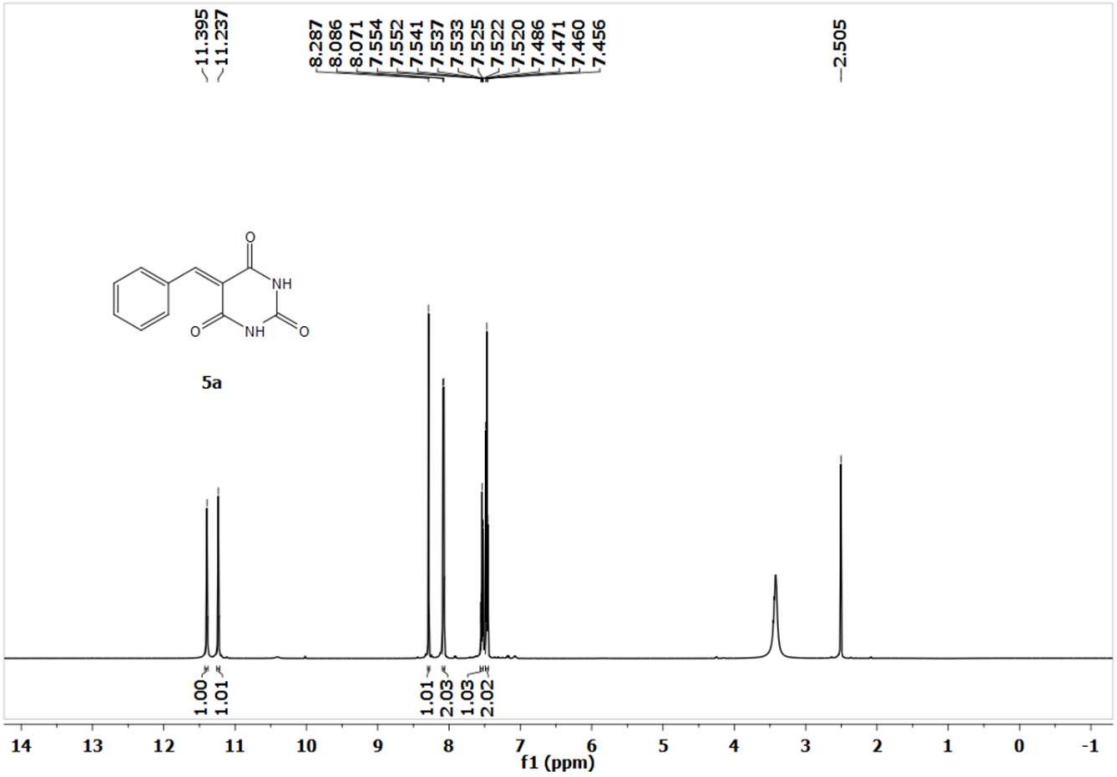


Figure 4.5 ^{1}H NMR of 5-Benzylidenebarbituric acid (5a)

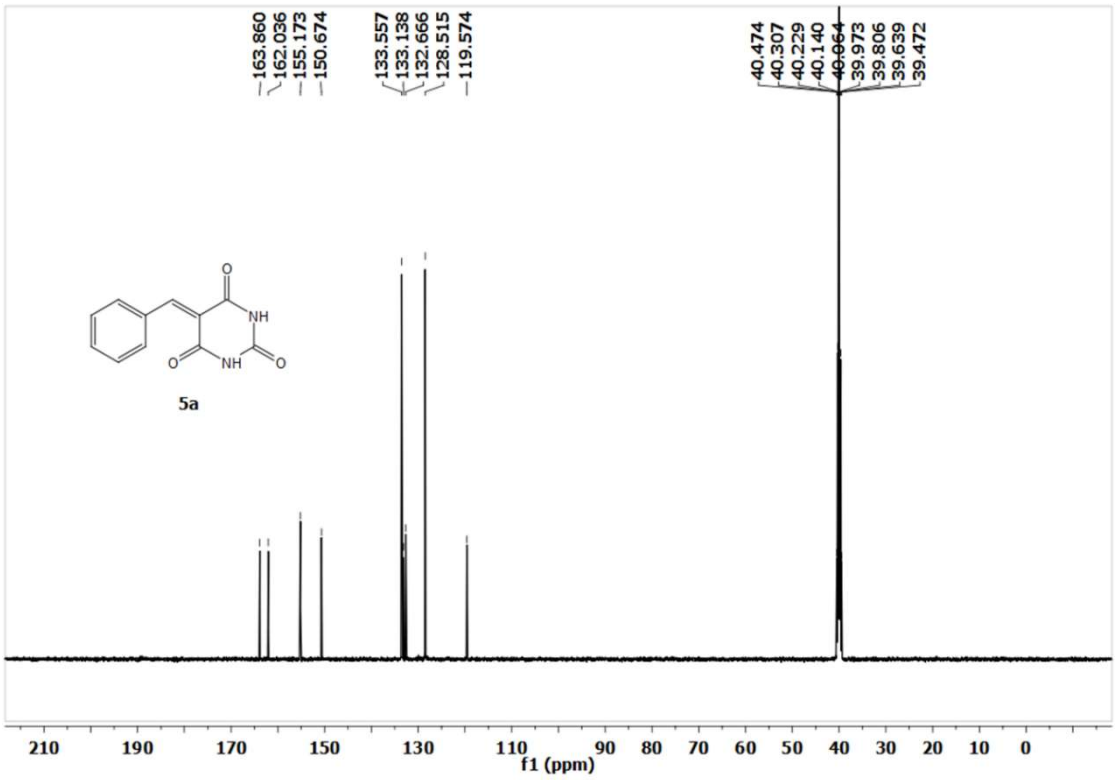


Figure 4.6 ^{13}C NMR of 5-Benzylidenebarbituric acid (5a)

4.4.5 Spectral Data of Product 5-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6a)

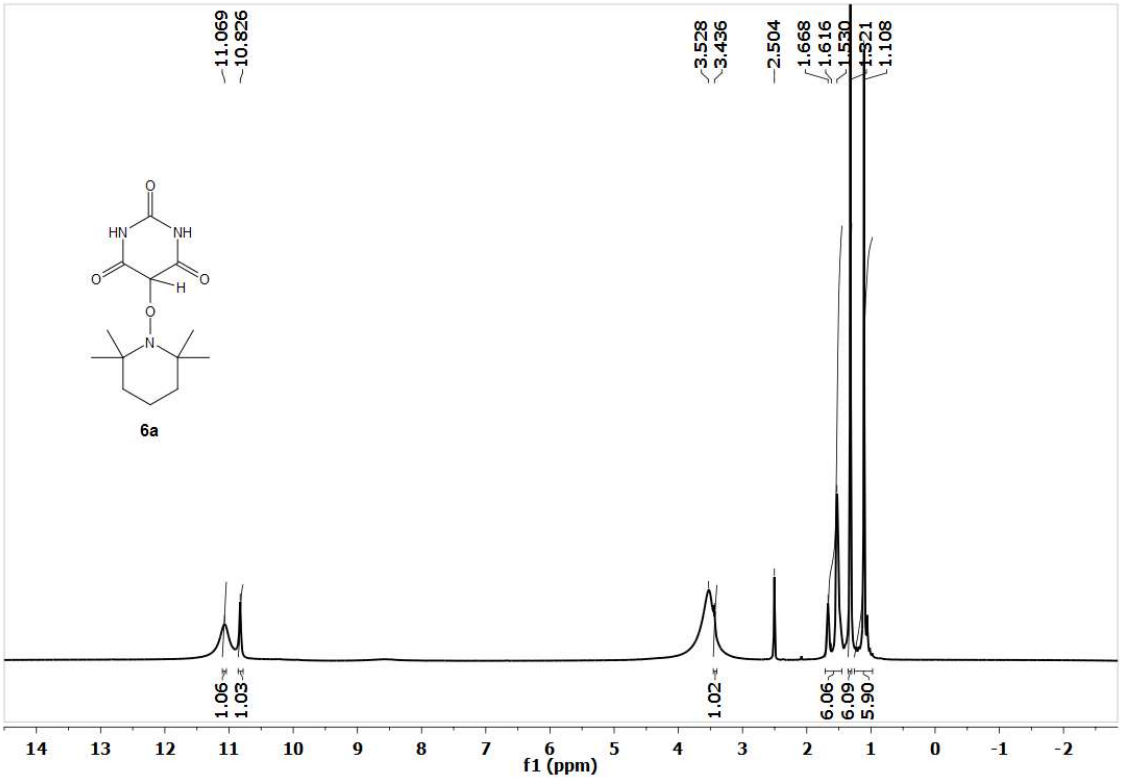


Figure 4.7 ^{1}H NMR 5-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6a)

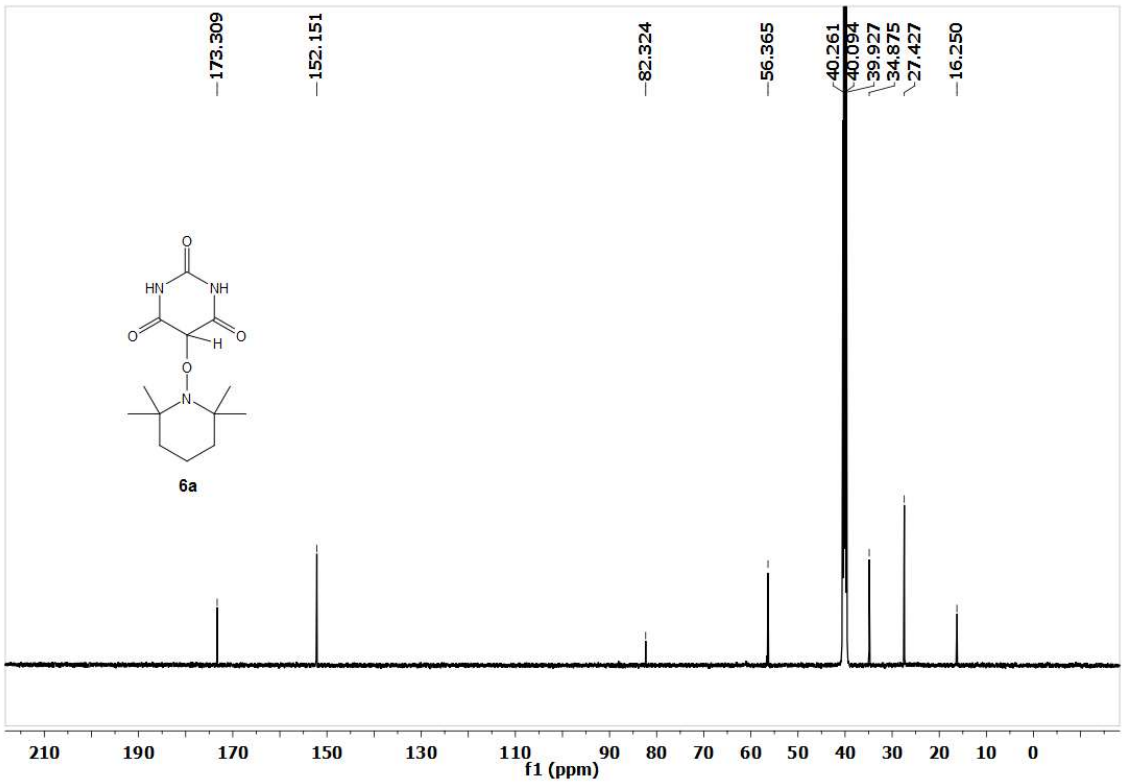


Figure 4.8 ^{13}C NMR of 5-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (6a)

4.4.6 UV Spectra of Compounds

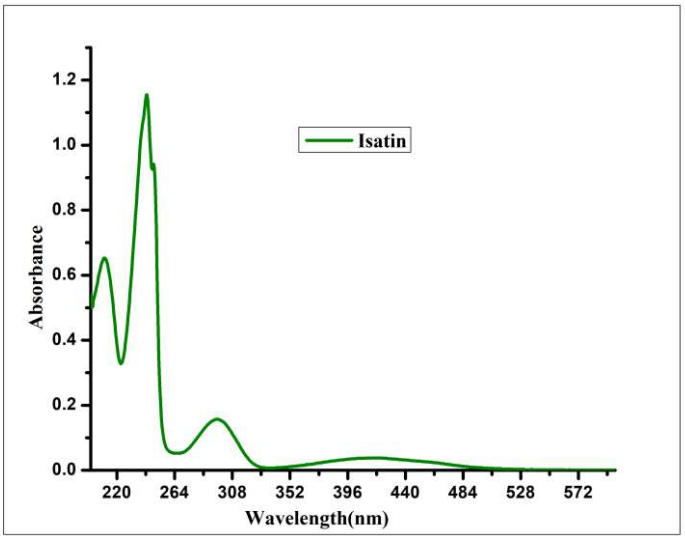


Figure 4.9 UV spectrum of isatin in ethanol (Conc. 2.5 x 10^{-4} mol/L)

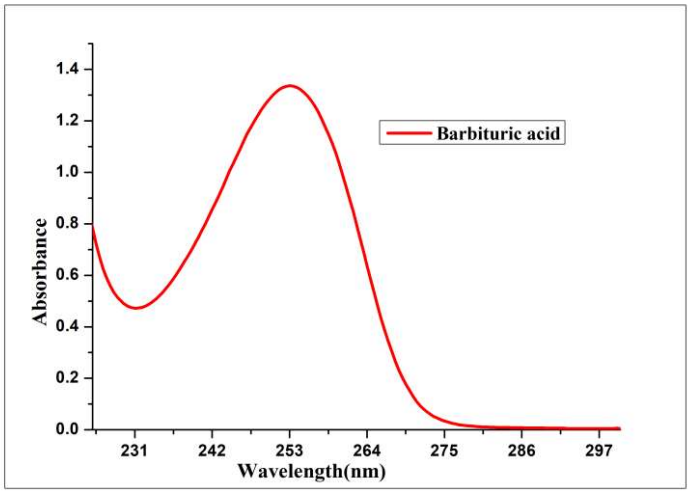


Figure 4.10 UV spectrum of barbituric acid in ethanol (Conc. 1.0 x 10^{-4} mol/L)

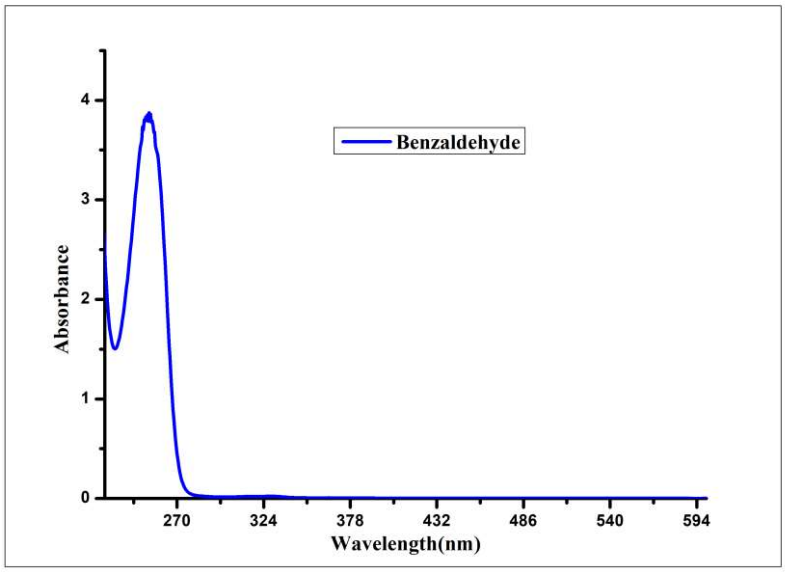


Figure 4.11 UV spectrum of benzaldehyde in ethanol (Conc. 1.5 x 10^{-4} mol/L)

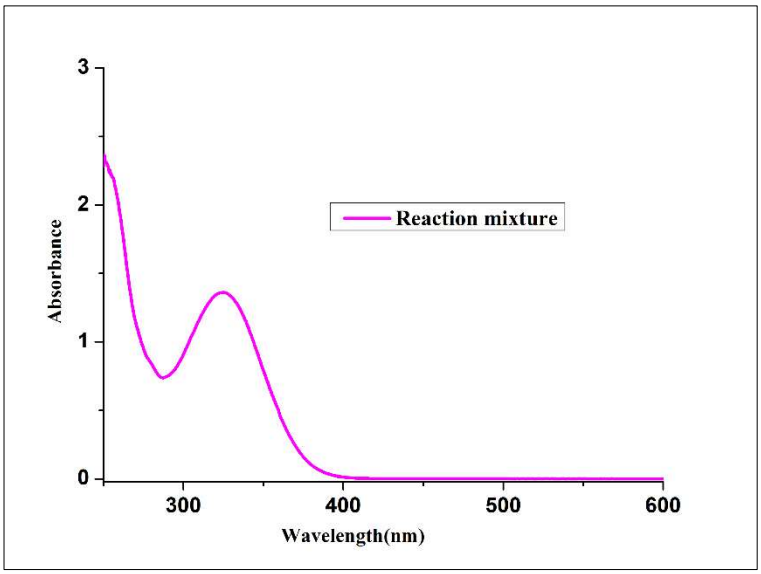


Figure 4.12 UV spectrum of reaction mixture (benzaldehyde and barbituric acid) in ethanol (Conc. 1.25 x 10^{-4} mol/L)

4.5 References

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