CHAPTER 5

Visible Light Mediated, Catalyst-free, One-Pot, Multicomponent Synthesis of Naphthopyranopyrimidines Under Aqueous Condition

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5.1 Introduction

Naphthopyranopyrimidine and its derivatives have gained the great interest of researchers because these compounds are extremely beneficial in biological and medicinal chemistry [1]. These compounds also display promising hypolipidemic [2], physiological [3], molluscicidal [4], antibacterial [5], antifungal [6], analgesic [7], anticonvulsant [8], and antitumor activities [9]. Currently, the biological activity of these molecules has been recognized in the treatment of anxiety, sleep, and addiction disorders. The neuropeptide S receptor, formerly known as GPR-154, is found in brain areas that have been associated with the modulation of anxiety, arousal, and stress. Consequently, neuropeptide S receptor is used to treat anxiety and sleep disorders [10]. Naphthopyranopyrimidines are the antagonists of neuropeptide S receptor (**Figure 5.1**).

Previously, naphthopyranopyrimidines have been synthesized by various methods using indium (III) chloride [11], formic acid [12], iodine [13], $Al(H_2PO_4)_3$ [14], ZnO nanoparticles [15], $H_4[SiW_{12}O_{40}]$ [16], alum $KAl(SO_4)_2.12H_2O$ [17], *L*-proline [18]. Nevertheless, some of these procedures often require expensive catalysts, harsh reaction conditions, and long reaction times. Therefore, there is a necessity to develop an efficient, cost-effective and simple protocol for the synthesis of naphthopyranopyrimidines of biological significance.

The visible light-mediated reaction has emerged as a flourishing, powerful method for the formation of bioactive compounds, as well as an evolving area of research to improve effectiveness and synthetic utility [19-22]. External photocatalysts (inorganic semiconductors [23], organic dyes [24, 25], transition metal complexes [26]) have traditionally been used to absorb visible light and initiate subsequent transformations. However, photocatalyst-free, visible light-initiated reactions have emerged as new innovations and opportunities for organic synthesis under moderate reaction conditions [27-34].

Multi-component reactions (MCRs) have emerged as a potent and incredible tool in contemporary synthetic chemistry to make various "drug-like" heterocyclic moieties due to their high merit of junction, high yields, output, ease of execution and environmental friendliness [35-40]. Multi-component reactions are effective method for rapidly and efficiently combining three or more starting materials into a single substance with a higher molecular weight. The multicomponent reactions are highly important in pharmaceutical chemistry due to their wide range of applications for preparation of variety of complex organic molecules [41-45].

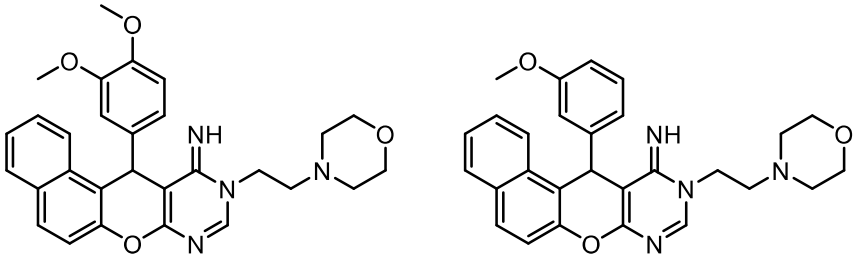
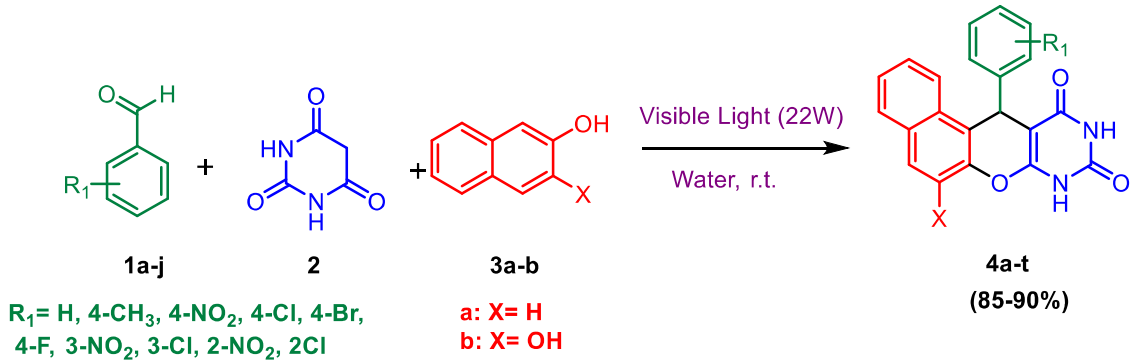


Figure 5.1 Antagonists of neuropeptide S receptor.

In continuation of our efforts to develop a green synthetic approach on the design and preparation of biologically active compounds [46, 47], herein we report additive- and photocatalyst-free one-pot, multicomponent synthesis of naphthopyranopyrimidines under visible light irradiation (**Scheme 5.1**).



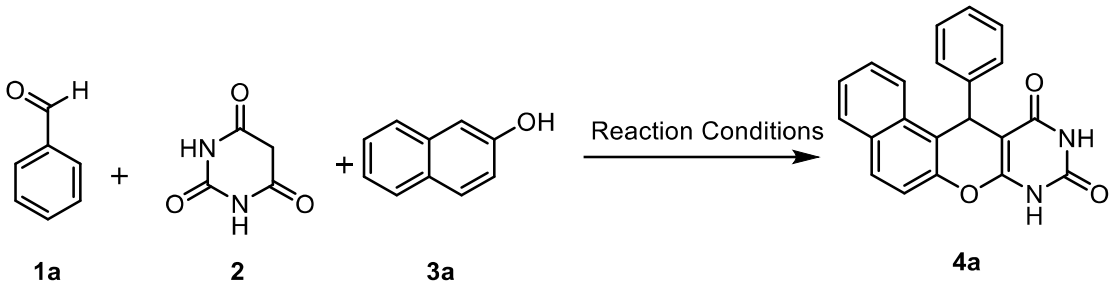
Scheme 5.1 Visible light-mediated synthesis of naphthopyranopyrimidines.

5.2 Results and Discussion

The optimization started by taking benzaldehyde (2.0 mmol), barbituric acid (2.0 mmol) and *β*- naphthol (2.0 mmol) as a model reaction by using 22 W white LED as a visible light source. Initially, water was chosen as the most environmentally friendly solvent for our system. When the screening of various acidic catalysts like sulfamic acid, *p*-TSA, *L*-proline and $AlCl_3$ were performed, 54%, 49%, 45%, and trace amount of the product **(4a)** was obtained respectively (**Table 5.1, entries 1-4**). Further, basic catalysts like Et_3N and *t*-BuOK were optimized and it was observed that 20% and trace amount of the product was found respectively (**Table 5.1, entries 5, 6**). Subsequently, screening of various photocatalysts like eosin-Y, acridine red and rhodamine-B was done but

unfortunately, they did not lead to a satisfactory amount of product (**Table 5.1, entries 7-9**). Now a series of solvents like acetonitrile, DCM, THF, EtOAc, glycerol, methanol, ethanol and water were tested under catalyst-free condition and surprisingly it was found that water exhibited promising result yielding 90% of the product (**Table 5.1, entry 17**). In the last, no product was obtained under catalyst-free and solvent-free condition **(Table 5.1, entry 18)**.

Table 5.1 Optimized reaction condition for the model reaction 4a[a]



Entry	Catalysts (mol %)	Solvent (5 ml)	Time(h)	Yield[b] (%)
1	Sulfamic Acid (10)	Water	8	54
2	*p*-TSA (10)	Water	8	49
3	*L*-Proline (10)	Water	8	45
4	$AlCl_3$ (10)	Water	8	Trace
5	Et_3N (10)	Water	8	20
6	*t*-BuOK (10)	Water	8	Trace
7	Eosin-Y (10)	Water	7	21

8	Acridine red (10)	Water	7	25
9	Rhodamine-B (10)	Water	7	28
10	-	Acetonitrile	10	N.R.
11	-	DCM	10	N.R.
12	-	THF	10	N.R.
13	-	EtOAc	10	Trace
14	-	Glycerol	10	Trace
15	-	Methanol	5	65
16	-	Ethanol	5	70
17	**-**	**Water**	**1.5**	**90**
18	-	Solvent-free	6	N.R.

[a]Reaction conditions: 1a (2.0 mmol), 2 (2.0 mmol), 3a (2.0 mmol), 22W white LED.
[b]Isolated yield
N.R.=no reaction

In order to find the optimum reaction condition, the effect of molar ratio of substrates on the yield of the product was investigated. The reactions of benzaldehyde, barbituric acid, and β - naphthol were thoroughly carried out by changing their molar proportions (**Tables 5.2**). The examination of **Table 5.2** reveals that the best result was found by using benzaldehyde, barbituric acid, and β - naphthol in the molar proportions 1.0:1.0:1.0. (**Table 5.2, entry 1**).

Table 5.2 Effect of the molar ratio of substrates on the yield of the product **4a.**[a]

Entry	Molar ratio of reactants (benzaldehyde:barbituric acid:*β*- naphthol)	%Yield[b]
1	**1:1:1**	**90**
2	1:2:1	85
3	2:1:1	41
4	1:1:2	79

[a]Reaction conditions: benzaldehyde (1a), barbituric acid (2), *β*- naphthol (3a), water (5 ml), 22W white LED, 1.5h.
[b]Isolated yield

To determine the optimum intensity of visible light, the reaction of benzaldehyde, barbituric acid, and *β* - naphthol was carried out at various intensities of visible light (12W, 15W, 20W, 22W, and 30W), as shown in **Table 5.3**. The best result was obtained with 22 W white LED **(Table 5.3, entry 4)**.

Table 5.3 Effect of the visible light intensity on the direction of the reaction **4a**.[a]

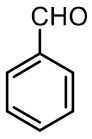
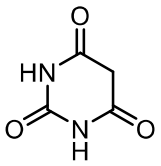
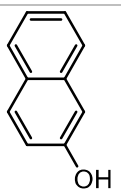
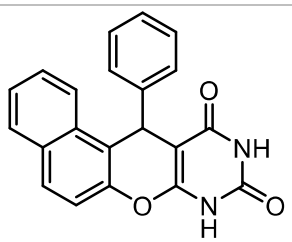
Entry	Visible light Intensity	Time (h)	Yield (%)[b]
1	12 W	6	51
2	15 W	7	59
3	20W	7	75
4	**22 W**	**1.5**	**90**
5	30 W	1.5	90

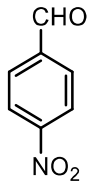
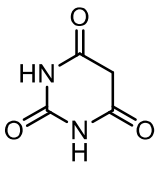
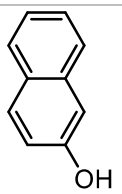
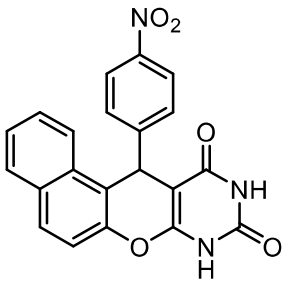
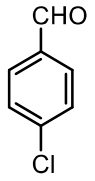
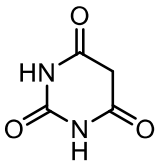
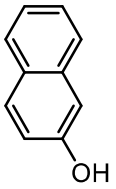
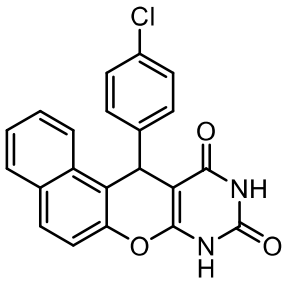
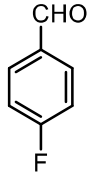
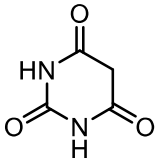
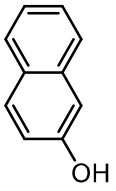
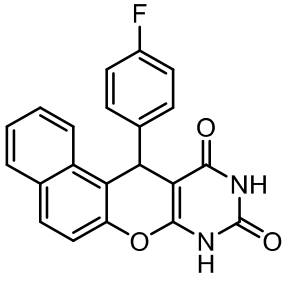
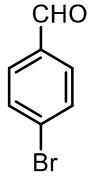
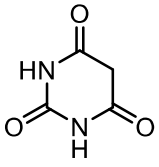
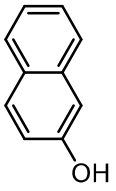
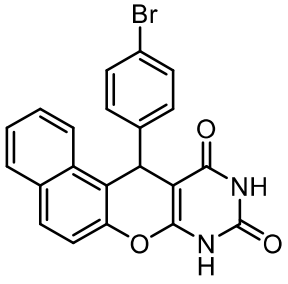
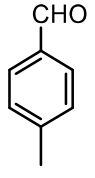
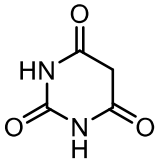
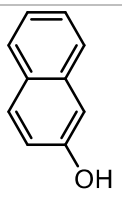
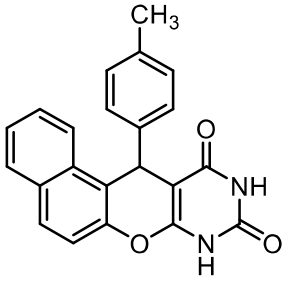
[a]Reaction conditions: 1a (2.0 mmol), 2 (2.0 mmol), 3a (2.0 mmol), water (5 ml).
[b]Isolated yield

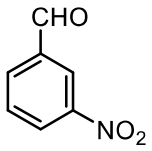
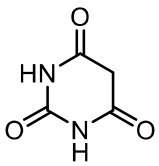
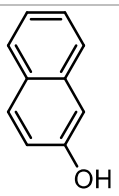
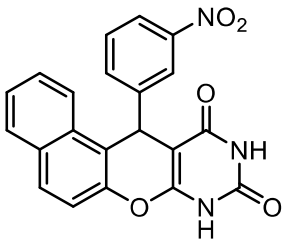
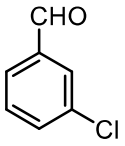
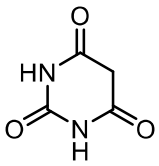
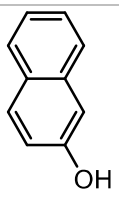
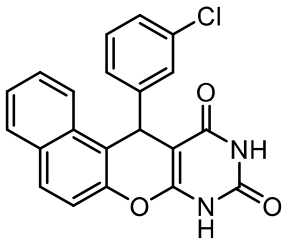
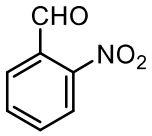
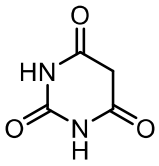
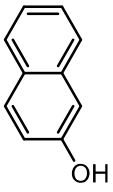
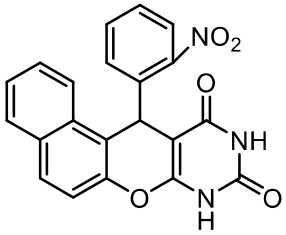
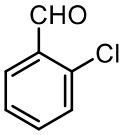
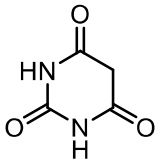
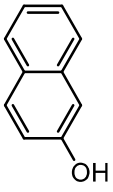
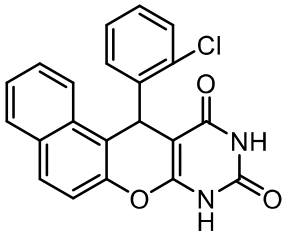
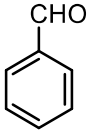
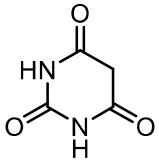
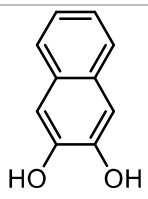
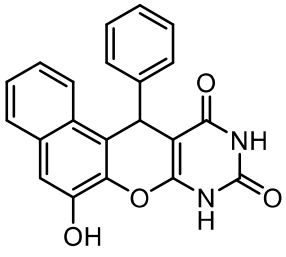
However, at lower intensities, low yield of the product was observed over a long period of time (**Table 5.3, entries 1, 2, 3**). In contrast, using a higher intensity of white LED (30 W) has no effect on product yield or reaction time **(Table 5.3, entry 5)**.

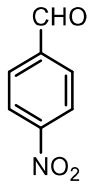
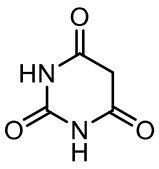
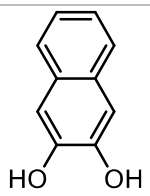
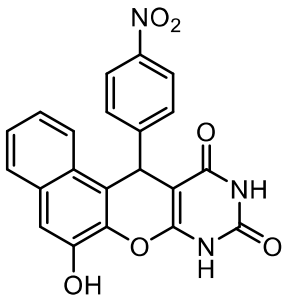
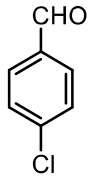
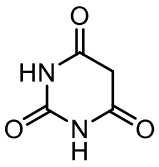
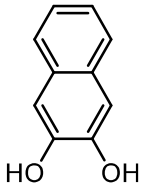
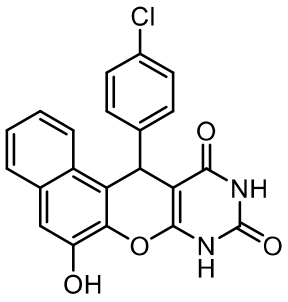
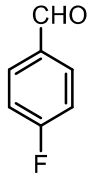
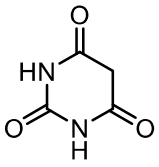
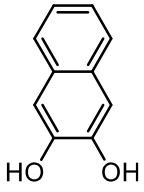
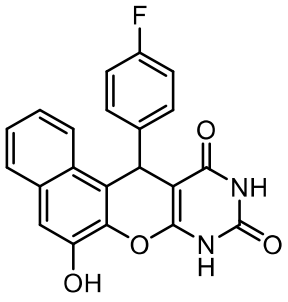
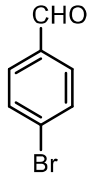
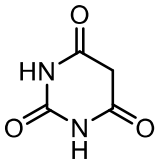
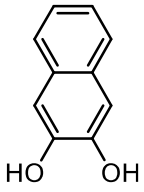
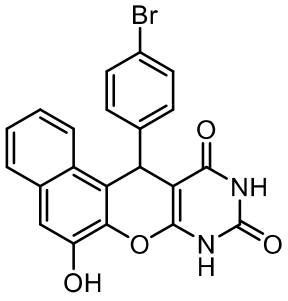
To extend the scope of this methodology, a broad range of substituted aryl aldehydes like benzaldehyde **(1a)**, 4-nitrobenzaldehyde **(1b)**, 4-chlorobenzaldehyde **(1c)**, 4-fluorobenzaldehyde **(1d)**, 4-bromobenzaldehyde **(1e)**, 4-methylbenzaldehyde **(1f)**, 3-nitrobenzaldehyde **(1g)**, 3-chlorobenzaldehyde **(1h)**, 2-nitrobenzaldehyde **(1i)**, 2-chlorobenzaldehyde **(1j)** i.e., both electron-withdrawing and electron-donating groups, were investigated under optimum conditions with barbituric acid **(2)** and *β* - naphthol **(3a)** / 2, 3 dihydroxynaphthalene **(3b)**. They worked efficiently to yield the products in high yields (85-90 %) **(Table 5.4)**.

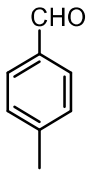
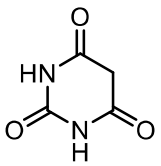
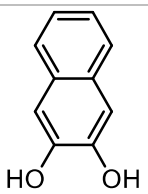
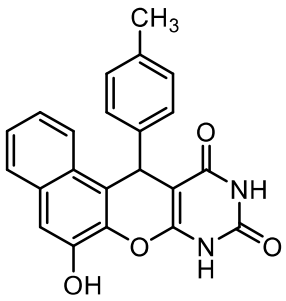
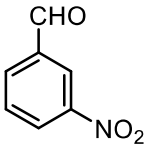
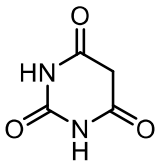
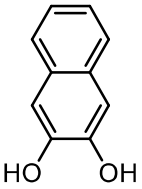
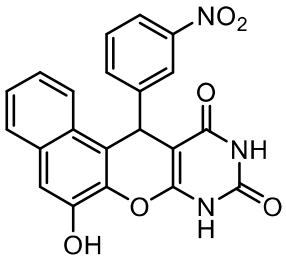
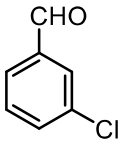
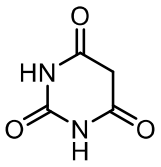
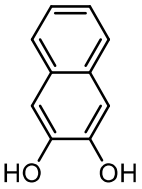
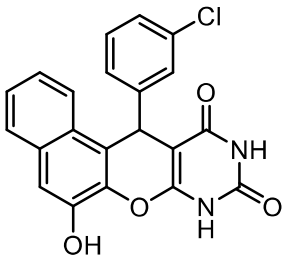
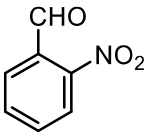
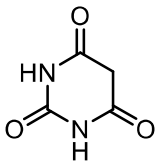
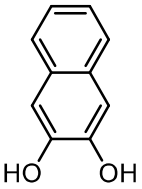
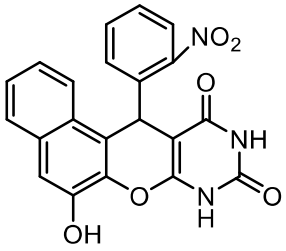
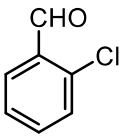
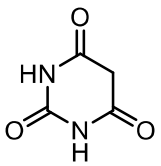
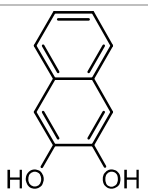
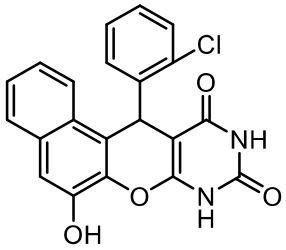
Table 5.4 Screening of substrates for the synthesis of naphthopyranopyrimidines.[a]

Entry	1	2	3	4[a]	Yield[b] (%)
4a	 **1a**		 **3a**		**90**

4b	 **1b**		 **3a**		**86**
4c	 **1c**		 **3a**		**89**
4d	 **1d**		 **3a**		**85**
4e	 **1e**		 **3a**		**88**
4f	 **1f**		 **3a**		**87**

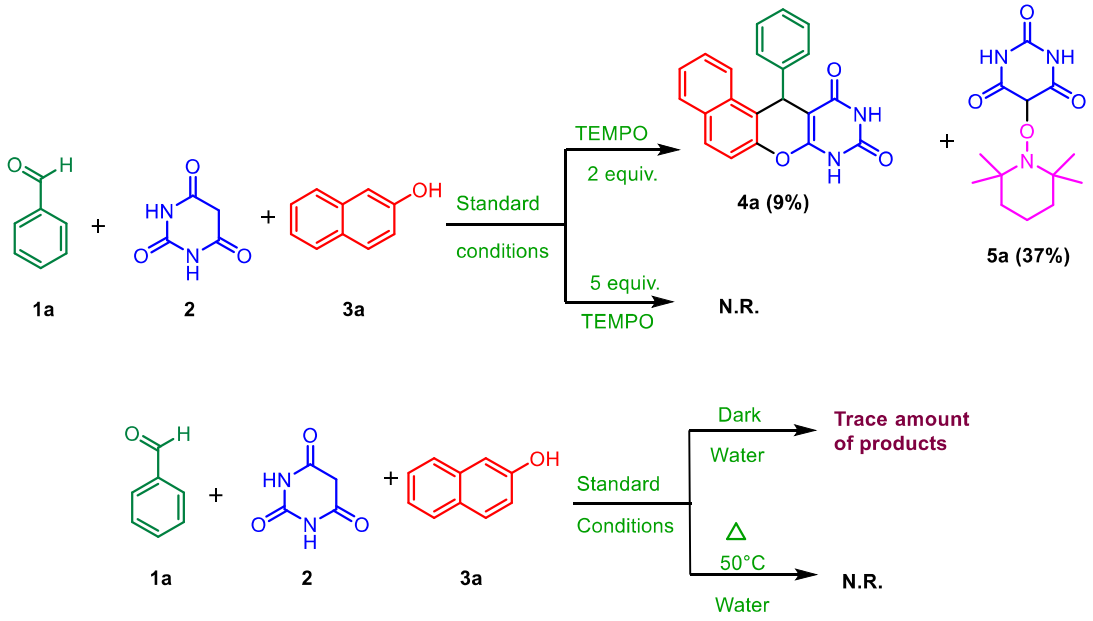
4g	 **1g**		 **3a**		**85**
4h	 **1h**		 **3a**		**89**
4i	 **1i**		 **3a**		**86**
4j	 **1j**		 **3a**		**88**
4k	 **1a**		 **3b**		**85**

4l	 **1b**		 **3b**		**89**
4m	 **1c**		 **3b**		**87**
4n	 **1d**		 **3b**		**90**
4o	 **1e**		 **3b**		**85**

4p	 **1f**		 **3b**		**88**
4q	 **1g**		 **3b**		**86**
4r	 **1h**		 **3b**		**89**
4s	 **1i**		 **3b**		**87**
4t	 **1j**		 **3b**		**85**

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

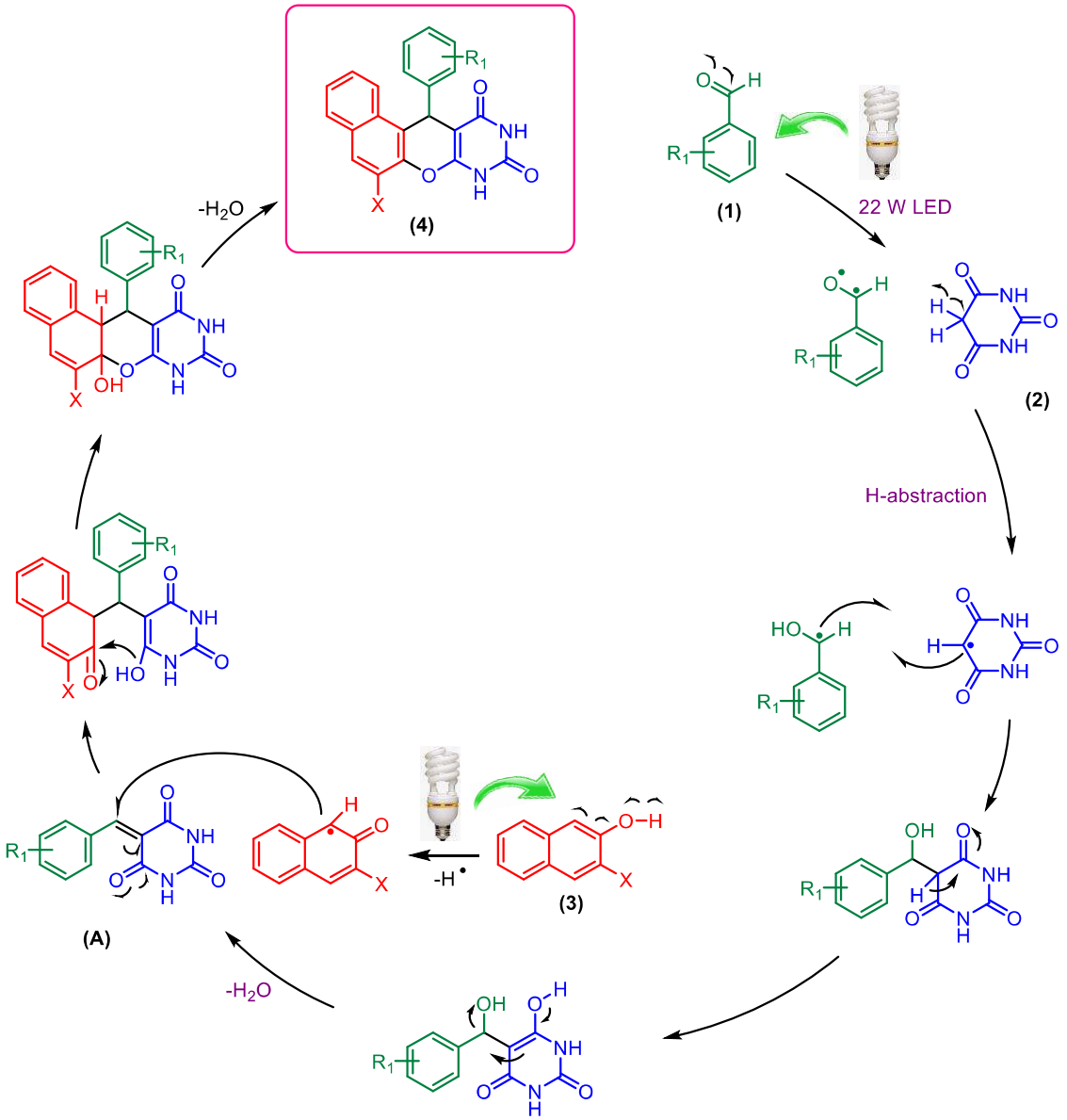
To determine the reaction mechanism, some control experiments were performed. It was established that free-radical species participated in the reaction, by performing a quenching experiment with a radical scavenger, TEMPO (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl. Under standard conditions, the model reaction yielded the corresponding products **4a** in 9% yield in the presence of 2 equivalents of TEMPO, while the product formation was completely quenched with 5 equivalents of TEMPO. Thus, the inhibitory action of TEMPO approved the participation of a radical intermediate in this reaction (**Scheme 5.2**). The formation of the adduct 5-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione **(5a)**, which was characterised by ^{1}H and ^{13}C NMR spectral data, further established the participation of a free radical species in the mechanism. A trace amount of product was found in the absence of visible light, i.e., in the dark at room temperature, however, no product was formed when the same



Scheme 5.2 Control experiments to establish the mechanism of reaction.

reaction was carried out at 50°C. These two results highlight the significance of visible light in this reaction **(Scheme 5.2)**.

Based on the reported literature [48], isolated product, UV spectra, and controlled experiment, **Scheme 5.3** represents a plausible reaction mechanism for the synthesis of naphthopyranopyrimidine derivatives **(4)**. Primarily, free radical of aryl aldehyde **(1)**



Scheme 5.3 Plausible mechanism for the synthesis of naphthopyranopyrimidines.

developed with irradiation of visible light. This free radical abstract hydrogen radical from barbituric acid **(2)**, and the formation of **(A)** take place after the removal of H_2O. The formation of **(A)** was confirmed by its ^{1}H and ^{13}C NMR spectra. Then, after irradiation, β - naphthol/ 2, 3 dihydroxynaphthalene **(3)** forms a free radical and reacts with intermediate **(A)** to produce the desired product **(4)**.

5.3 Conclusion

A practical and efficient procedure for the synthesis of naphthopyranopyrimidines has been reported by reaction of β-naphthol/ 2,3-dihydroxynaphthalene, barbituric acid, and aromatic aldehydes in aqueous medium under visible light irradiation. The reaction proceeds under additive- and photocatalyst-free conditions to produce the desired products in good to excellent yields with a wide range of substrate scope. This approach has advantages in terms of easy workup, operational simplicity, and short reaction times. This protocol meets the requirements of sustainable chemistry and provides a significant opportunity for the development of other multi-component reactions for building synthetically and biologically important moieties under visible-light irradiation.

5.4 Experimental Section

5.4.1 General Procedure for the Synthesis of Naphthopyranopyrimidines (4a-t)

Benzaldehyde (2.0 mmol), barbituric acid (2.0 mmol) and β-naphthol/ 2,3 dihydroxynaphthalene (2.0 mmol) were stirred at room temperature under irradiation of 22 W white LED by using water (5 ml) as a solvent. After the completion of reaction

(monitored by TLC), the reaction mixture was filtered to yield the solid product. Then, crude product was recrystallized from ethanol to afford the pure product **(4a-t)**.

5.4.2 Analytical Data

12-Phenyl-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4a) White solid (90% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3483, 3032, 1707, 1676, 1255; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.06 (s, 1H,NH), 7.99 - 7.90 (m, 3H, Ar-H), 7.49 - 7.41 (m, 3H, Ar-H), 7.29 (d, *J* = 7.3 Hz, 2H, Ar-H), 7.18 (t, *J* = 7.7 Hz, 2H, Ar-H), 7.07 (t, *J* = 7.3 Hz, 1H, Ar-H), 5.56 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.33, 153.65, 149.77, 146.86, 144.73, 131.44, 130.54, 129.86, 128.81, 128.44, 128.26, 127.59, 126.68, 125.50, 123.78, 117.22, 90.02, 34.81; **Anal. Calc. for $C_{21}H_{14}N_2O_3$:** C, 73.68; H, 4.12; N, 8.18; Found: C, 73.88.; H, 4.35; N, 8.31.

12-(4-Nitrophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4b) White solid (86% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3446, 2927, 1704, 1669, 1230; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 12.20 (s, 1H,NH), 11.12 (s, 1H,NH), 8.10 - 8.04 (m, 2H, Ar-H), 8.03 - 8.00 (m, 1H, Ar-H), 7.96 (m, 2H, Ar-H), 7.64 - 7.58 (m, 2H, Ar-H), 7.52 - 7.43 (m, 3H, Ar-H), 5.77 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.49, 154.12, 152.28, 149.99, 147.16, 146.49, 131.73, 130.69, 130.02, 129.17, 128.08, 125.95, 124.00, 123.90, 117.27, 116.18, 89.08, 35.17; **Anal. Calc. for $C_{21}H_{13}N_3O_5$:** C, 65.12; H, 3.38; N, 10.85; Found: C, 65.28.; H, 3.32; N, 10.71.

12-(4-Chlorophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4c) White solid (89% yield); mp: 288-290°C; **IR (KBr)** *v* cm^{-1}: 3458, 3208, 3058, 2867, 1704, 1680, 1225; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.43 (s, 1H,NH), 11.28 (s, 1H,NH), 8.06 (d, *J* = 8.5 Hz, 3H, Ar-H), 7.98 - 7.92 (m, 2H, Ar-H), 7.52 - 7.48 (m, 3H, Ar-H), 7.33 - 7.25 (m, 2H, Ar-H), 5.59 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.68, 153.52, 150.65, 147.10, 143.93, 137.21, 135.13, 132.00, 131.64, 130.44, 129.82, 129.10, 128.61, 128.54, 125.84, 124.02, 120.09, 116.89, 89.77, 34.58; **Anal. Calc. for $C_{21}H_{13}ClN_2O_3$:** C, 66.94; H, 3.48; N, 7.43; Found: C, 66.86.; H, 3.62; N, 7.59.

12-(4-Fluorophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4d) White solid (85% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3481, 3197, 2855, 1703, 1672, 1267; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 11.41 (s, 1H,NH), 11.08 (s, 1H,NH), 8.28 (s, 1H, Ar-H), 8.25 - 8.22 (m, 1H, Ar-H), 8.02 - 7.98 (m, 2H, Ar-H), 7.52 - 7.45 (m, 2H, Ar-H), 7.36 - 7.31 (m, 3H, Ar-H), 7.04 - 7.00 (m, 1H, Ar-H), 5.62 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.87, 153.88, 150.02, 147.11, 141.24, 136.86, 132.81, 131.73, 130.77, 130.25, 129.10, 127.88, 125.81, 124.12, 119.18, 116.94, 90.04, 34.39; **Anal. Calc. for $C_{21}H_{13}FN_2O_3$:** C, 70.00; H, 3.64; N, 7.77; Found: C, 70.18.; H, 3.52; N, 7.54.

12-(4-Bromophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4e) White solid (88% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3488, 3207, 3043, 2898, 1707, 1673, 1228; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 12.10

(s, 1H,NH), 11.09 (s, 1H,NH), 7.98 - 7.93 (m, 3H, Ar-H), 7.65 (d, *J* = 8.6 Hz, 1H, Ar-H), 7.48 - 7.42 (m, 2H, Ar-H), 7.37 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.26 (d, *J* = 8.5 Hz, 2H, Ar-H), 5.57 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 162.14, 154.04, 150.77, 147.23, 144.47, 135.25, 132.49, 131.67, 130.95, 130.84, 130.48, 129.24, 126.42, 124.13, 120.32, 116.94, 89.83, 34.79; **Anal. Calc. for $C_{21}H_{13}BrN_2O_3$:** C, 59.88; H, 3.11; N, 6.65; Found: C, 59.58.; H, 3.32; N, 6.71.

12-(*p*-Tolyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4f) Yellowish solid (87% yield); mp:260-262°C; **IR (KBr)** *v* cm^{-1}: 3430, 3181, 3014, 2902, 1708, 1681, 1238; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 12.07 (s, 1H,NH), 11.06 (s, 1H,NH), 7.99 - 7.90 (m, 3H, Ar-H), 7.51 - 7.38 (m, 3H, Ar-H), 7.17 (d, *J* = 8.1 Hz, 2H, Ar-H), 6.98 (d, *J* = 7.9 Hz, 2H, Ar-H), 5.52 (s, 1H,CH), 2.14 (s, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.56, 153.77, 150.04, 147.06, 142.13, 136.00, 131.68, 130.83, 130.00, 129.23, 129.03, 128.40, 127.76, 125.73, 124.10, 117.63, 117.13, 90.36, 34.67, 20.94; **Anal. Calc. for $C_{22}H_{16}N_2O_3$:** C, 74.15; H, 4.53; N, 7.86; Found: C, 74.38.; H, 4.62; N, 7.61.

12-(3-Nitrophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4g) Yellow solid (85% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3418, 3209, 3028, 1706, 1668, 1251; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 12.21 (s, 1H,NH), 11.15 (s, 1H,NH), 8.01 - 7.97 (m, 3H, Ar-H), 7.56 - 7.52(m, 4H, Ar-H), 7.27 - 7.22 (m, 3H, Ar-H), 5.60 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.87, 153.85, 150.05, 147.38, 147.20, 133.28, 131.55, 130.64, 129.25, 128.14, 127.54, 127.12,

125.36, 124.15, 117.24, 116.37, 89.56, 34.27; **Anal. Calc. for $C_{21}H_{13}N_3O_5$:** C, 65.12; H, 3.38; N, 10.85; Found: C, 65.38.; H, 3.42; N, 10.63.

12-(3-Chlorophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4h) White solid (89% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3395, 3221, 3013, 1705, 1658, 1267; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 12.14 (s, 1H,NH), 11.12 (s, 1H,NH), 7.99 - 7.93 (m, 3H, Ar-H), 7.50 - 7.42 (m, 4H, Ar-H), 7.20 - 7.14 (m, 3H, Ar-H), 5.62 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.53, 153.99, 150.01, 147.32, 147.21, 133.19, 131.70, 130.73, 130.61, 129.10, 128.43, 127.99, 127.01, 125.87, 124.08, 117.18, 116.65, 89.61, 34.85; **Anal. Calc. for $C_{21}H_{13}ClN_2O_3$:** C, 66.94; H, 3.48; N, 7.43; Found: C, 66.78.; H, 3.69; N, 7.21.

12-(2-Nitrophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4i) White solid (86% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3429, 3125, 2917, 1709, 1669, 1236; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 12.07(s, 1H,NH), 11.25 (s, 1H,NH), 8.05- 7.98 (m, 4H, Ar-H), 7.59 - 7.55 (m, 3H, Ar-H), 7.49 - 7.46 (m, 3H, Ar-H), 5.86 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.60, 154.21, 152.21, 150.01, 147.25, 146.36, 131.88, 130.85, 130.32, 129.89, 129.27, 128.62, 128.04, 126.29, 123.42, 117.78, 116.23, 89.57, 35.09; **Anal. Calc. for $C_{21}H_{13}N_3O_5$:** C, 65.12; H, 3.38; N, 10.85; Found: C, 65.48.; H, 3.22; N, 10.59.

12-(2-Chlorophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4j) White solid (88% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3469, 3138, 2926, 1707, 1657, 1246; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 12.08 (s, 1H,NH),

11.26 (s, 1H,NH), 8.00 - 7.85 (m, 4H, Ar-H), 7.51 - 7.45 (m, 3H, Ar-H), 7.41 - 7.36(m, 3H, Ar-H), 5.51 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.03, 153.91, 150.00, 147.23, 143.86, 137.16, 135.21, 132.02, 131.55, 130.73, 129.75, 128.76, 127.92, 125.72, 124.18, 120.77, 117.18, 90.24, 34.58; **Anal. Calc. for $C_{21}H_{13}ClN_2O_3$:** C, 66.94; H, 3.48; N, 7.43; Found: C, 66.68.; H, 3.62; N, 7.61.

6-Hydroxy-12-phenyl-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4k) Yellowish solid (85% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}:3498, 3214, 3066, 2862, 1702, 1643, 1268; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 12.07 (s, 1H,NH), 11.05 (s, 1H,NH), 10.57 (s, 1H,OH), 7.87 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.69 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.34 - 7.18 (m, 7H, Ar-H), 7.10 - 7.07 (m, 1H, Ar-H), 5.56 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.54, 153.93, 149.98, 145.57, 145.06, 139.56, 132.13, 128.70, 128.43, 126.99, 126.88, 125.94, 124.90, 124.41, 123.91, 119.14, 110.54, 90.19, 35.23; **Anal. Calc. for $C_{21}H_{14}N_2O_4$:** C, 70.39; H, 3.94; N, 7.82; Found: C, 70.48.; H, 3.67; N, 7.51.

6-Hydroxy-12-(4-nitrophenyl)-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4l) Yellowish solid (89% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}:3501, 3198, 2887, 1705, 1667, 1253; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 12.18 (s, 1H,NH), 11.13 (s, 1H,NH), 10.61 (s, 1H,OH), 8.06 - 8.03 (m, 3H, Ar-H), 7.79 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.67 (d, *J* = 8.7 Hz, 1H, Ar-H), 7.58 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.31 - 7.23 (m, 2H, Ar-H), 5.71 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.55, 154.14, 152.21, 149.98, 146.45, 145.51, 139.56, 132.13, 129.85, 128.53, 127.06,

126.13, 124.68, 123.91, 123.71, 117.65, 111.15, 89.02, 35.32; **Anal. Calc. for $C_{21}H_{13}N_3O_6$:** C, 62.53; H, 3.25; N, 10.42; Found: C, 62.38.; H, 3.37; N, 10.29.

12-(4-Chlorophenyl)-6-hydroxy-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4m) Yellow solid (87% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}:3497, 3097, 2876, 1702, 1654, 1262; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 12.09 (s, 1H,NH), 11.07 (s, 1H,NH), 10.58 (s, 1H,OH), 8.01 - 7.96 (m, 1H, Ar-H), 7.85 - 7.81 (m, 1H, Ar-H), 7.57 - 7.51 (m, 2H, Ar-H), 7.33 - 7.24 (m, 5H, Ar-H), 5.58 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.69, 153.95, 150.66, 147.96, 145.55, 139.55, 132.13, 132.03, 129.80, 128.64, 127.03, 125.99, 124.78, 124.50, 123.86, 118.51, 110.73, 89.70, 34.72; **Anal. Calc. for $C_{21}H_{13}ClN_2O_4$**: C, 64.21; H, 3.34; N, 7.13; Found: C, 64.38.; H, 3.57; N, 7.29.

12-(4-Fluorophenyl)-6-hydroxy-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4n) White solid (90% yield); mp: 278-280°C; **IR (KBr)** *v* cm^{-1}:3499, 3073, 2849, 1703, 1633, 1232; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 12.07 (s, 1H,NH), 11.27 (s, 1H,NH), 10.58 (s, 1H,OH), 7.84 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.33 - 7.26 (m, 6H, Ar-H), 7.04 - 7.00 (m, 2H, Ar-H), 5.58 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.57, 153.91, 150.67, 147.75, 145.68, 139.54, 132.15, 130.32, 130.26, 128.37, 127.02, 125.97, 124.80, 124.47, 123.90, 118.85, 110.64, 89.99, 34.53; **Anal. Calc. for $C_{21}H_{13}FN_2O_4$:** C, 67.02; H, 3.48; N, 7.44; Found: C, 67.18.; H, 3.24; N, 7.59.

12-(4-Bromophenyl)-6-hydroxy-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4o) Yellowish solid (85% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}:3482, 3208, 3045, 2854, 1708, 1675, 1262; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 12.10 (s, 1H,NH), 11.09 (s, 1H,NH), 10.59 (s, 1H,OH), 7.82 (d, *J* = 8.1 Hz, 1H, Ar-H, Ar-H), 7.70 (d, *J* = 8.3 Hz, 1H, Ar-H), 7.40 - 7.26 (m, 7H, Ar-H), 5.57 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.55, 153.95, 149.97, 145.56, 144.39, 139.55, 135.16, 132.14, 131.57, 130.73, 127.04, 126.01, 124.78, 124.52, 123.86, 119.99, 110.75, 89.64, 34.81; **Anal. Calc. for $C_{21}H_{13}BrN_2O_4$:** C, 57.69; H, 3.00; N, 6.41; Found: C, 57.41.; H, 3.24; N, 6.19.

6-Hydroxy-12-(*p*-tolyl)-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4p) Yellowish solid (88% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}:3489, 3144, 2934, 1706, 1659, 1243; **^{1}H NMR (500 MHz, DMSO-d_6) δ (ppm)=** 12.03 (s, 1H,NH), 11.03 (s, 1H,NH), 10.54 (s, 1H,OH), 7.96 - 7.84 (m, 3H, Ar-H), 7.30 - 7.14 (m, 4H, Ar-H), 6.99 (d, *J* = 7.7 Hz, 2H, Ar-H), 5.51 (s, 1H,CH), 2.15 (s, 3H,CH_3). **^{13}C NMR (126 MHz, DMSO-d_6) δ (ppm)=** 163.54, 153.82, 149.98, 145.55, 143.93, 139.48, 135.96, 132.11, 130.18, 128.29, 126.96, 125.89, 124.91, 124.36, 123.94, 118.32, 110.44, 90.28, 34.82, 20.96; **Anal. Calc. for $C_{22}H_{16}N_2O_4$:** C, 70.96; H, 4.33; N, 7.52; Found: C, 70.73.; H, 4.48; N, 7.39.

6-Hydroxy-12-(3-nitrophenyl)-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4q) White solid (86% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}:3491, 3156, 3071, 2861, 1701, 1683, 1249; **^{1}H NMR (500 MHz, DMSO-d_6) δ**

(ppm)= 12.17 (s, 1H,NH), 11.11 (s, 1H,NH), 10.65 (s, 1H,OH), 8.01 - 7.94 (m, 2H, Ar-H), 7.84 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.80 - 7.74 (m, 2H, Ar-H), 7.70 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.38 - 7.30 (m, 2H, Ar-H), 7.27 - 7.20 (m, 1H, Ar-H), 5.78 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.57, 154.13, 149.96, 148.13, 146.94, 145.55, 139.75, 135.19, 132.16, 130.20, 127.09, 126.10, 124.70, 123.87, 122.97, 117.72, 111.13, 89.19, 35.06; **Anal. Calc. for $C_{21}H_{13}N_3O_6$:** C, 62.53; H, 3.25; N, 10.42; Found: C, 62.65.; H, 3.54; N, 10.63.

12-(3-Chlorophenyl)-6-hydroxy-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4r) White solid (89% yield); mp>300^{o}C; **IR (KBr)** *v* cm^{-1}:3510, 3167, 3045, 2983, 2861, 1706, 1645, 1263; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 12.12 (s, 1H,NH), 11.10 (s, 1H,NH), 10.60 (s, 1H,OH), 7.85 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.71 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.40 - 7.16 (m, 7H, Ar-H), 5.61 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.55, 154.06, 149.97, 147.33, 145.54, 139.66, 133.21, 132.14, 130.64, 128.27, 127.13, 127.05, 127.00, 126.05, 124.78, 124.60, 123.88, 118.26, 110.88, 89.56, 35.00; **Anal. Calc. for $C_{21}H_{13}ClN_2O_4$:** C, 64.21; H, 3.34; N, 7.13; Found: C, 64.43.; H, 3.51; N, 7.23.

6-Hydroxy-12-(2-nitrophenyl)-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4s) White solid (87% yield); mp>300^{o}C; **IR (KBr)** *v* cm^{-1}:3493, 3164, 3056, 2948, 2878, 1704, 1676, 1234; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 12.14 (s, 1H,NH), 11.06 (s, 1H,NH), 10.59 (s, 1H,OH), 8.00 - 7.95 (m, 2H, Ar-H), 7.84 - 7.74 (m, 2H, Ar-H), 7.68 - 7.61 (m, 2H, Ar-H), 7.53 - 7.46 (m, 2H, Ar-H), 7.39

- 7.36 (m, 1H, Ar-H), 5.73 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.74, 154.27, 150.45, 148.91, 146.78, 145.34, 139.64, 134.98, 132.32, 129.65, 127.53, 126.21, 124.72, 123.56, 123.42, 117.78, 111.41, 89.00, 35.01; **Anal. Calc. for $C_{21}H_{13}N_3O_6$:** C, 62.53; H, 3.25; N, 10.42; Found: C, 62.29.; H, 3.31; N, 10.23.

12-(2-Chlorophenyl)-6-hydroxy-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4t) Yellowish solid (85% yield); mp>300°C; **IR (KBr)** *v* cm^{-1}: 3505, 3149, 3058, 2951, 2842, 1708, 1669, 1250; **^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)=** 12.17 (s, 1H,NH), 11.18 (s, 1H,NH), 10.62 (s, 1H,OH), 7.99 - 7.76 (m, 3H, Ar-H), 7.65 - 7.52 (m, 3H, Ar-H), 7.38 - 7.27 (m, 3H, Ar-H), 5.49 (s, 1H,CH). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.62, 153.38, 150.21, 147.81, 145.83, 139.69, 132.54, 132.10, 129.24, 128.52, 127.28, 126.02, 124.51, 124.28, 123.79, 118.12, 110.92, 89.61, 34.54; **Anal. Calc. for $C_{21}H_{13}ClN_2O_4$:** C, 64.21; H, 3.34; N, 7.13; Found: C, 64.53.; H, 3.57; N, 7.36.

5-Benzylidenebarbituric acid (A) ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)= 11.32 (s, 1H, NH), 11.15 (s, 1H, NH), 8.21(s, 1H,CH), 8.00 (d, 2H, Ar-H), 7.50- 7.45 (m, 1H, Ar-H), 7.38 - 7.34 (m, 2H, Ar-H). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 163.79, 162.00, 155.14, 150.60, 133.45, 133.21, 132.62, 128.49, 119.44.

5-((2,2,6,6-Tetramethylpiperidin-1-yl)oxy)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (5a) ^{1}H NMR (500 MHz, DMSO-*d*$_6$) δ (ppm)= 10.84 (s, 1H, NH), 9.62 (s, 1H, NH), 3.14 (s, 1H,CH), 1.67 - 1.42 (m, 6H,CH_2), 1.32 (s, 6H,CH_3), 1.12 (s, 6H,CH_3). **^{13}C NMR (126 MHz, DMSO-*d*$_6$) δ (ppm)=** 173.27, 150.93, 82.47, 56.38, 34.94, 27.53, 16.35.

5.4.3 Spectral Data of Product 12-(3-Chlorophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4h)

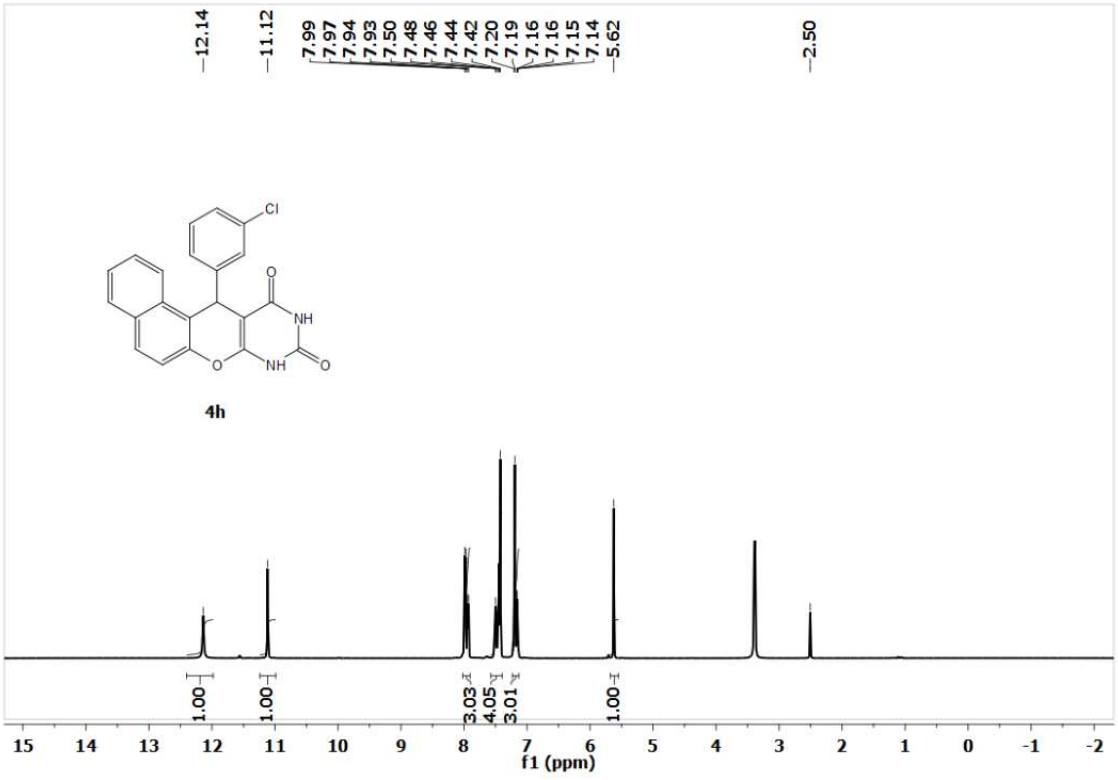


Figure 5.2 ^{1}H NMR of 12-(3-Chlorophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4h)

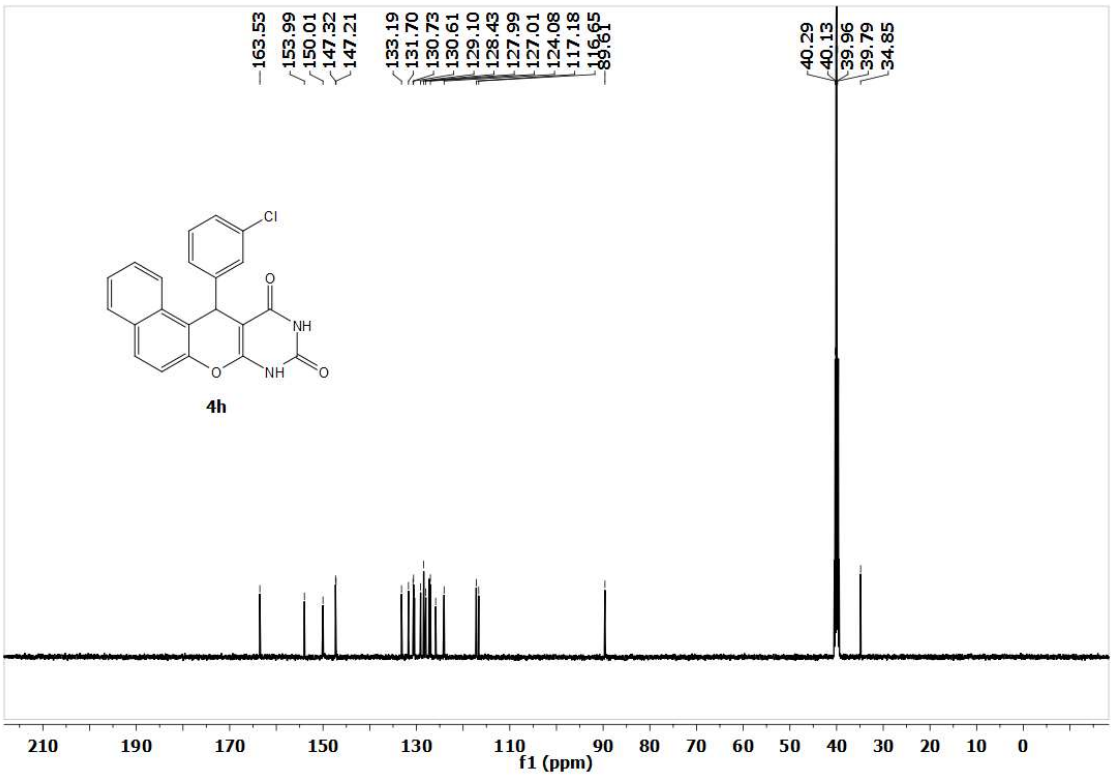


Figure 5.3 ^{13}C NMR of 12-(3-Chlorophenyl)- 8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4h)

5.4.4 Spectral Data of Product 6-Hydroxy-12-phenyl-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4k)

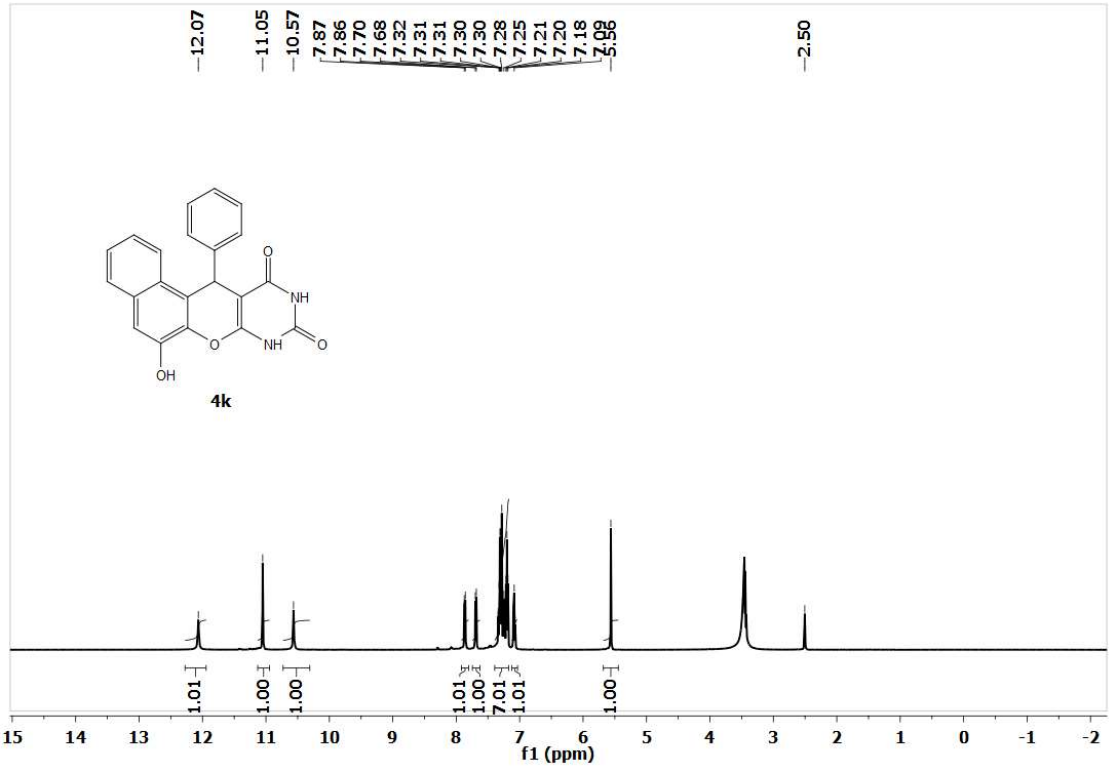


Figure 5.4 ^{1}H NMR of 6-Hydroxy-12-phenyl-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4k)

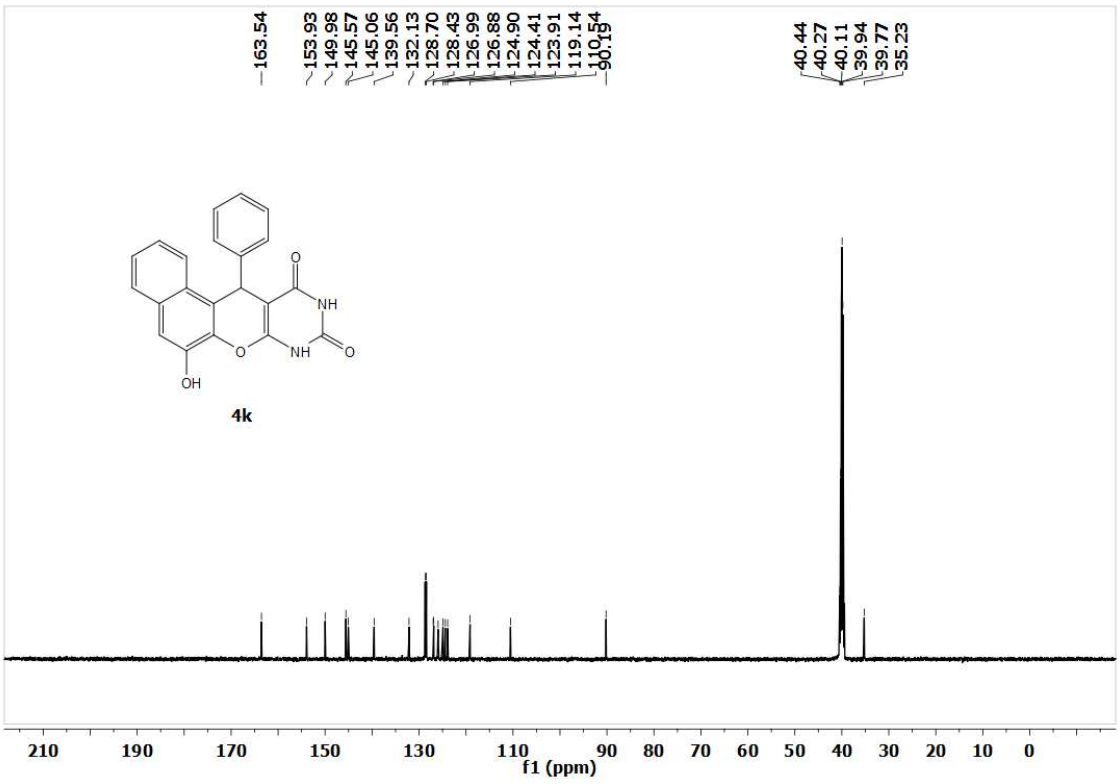


Figure 5.5 ^{13}C NMR of 6-Hydroxy-12-phenyl-8,12-dihydro-9*H*-naphtho[1',2':5,6]pyrano[2,3-*d*]pyrimidine-9,11-(10*H*)-dione (4k)

5.4.5 UV Spectra of Compounds

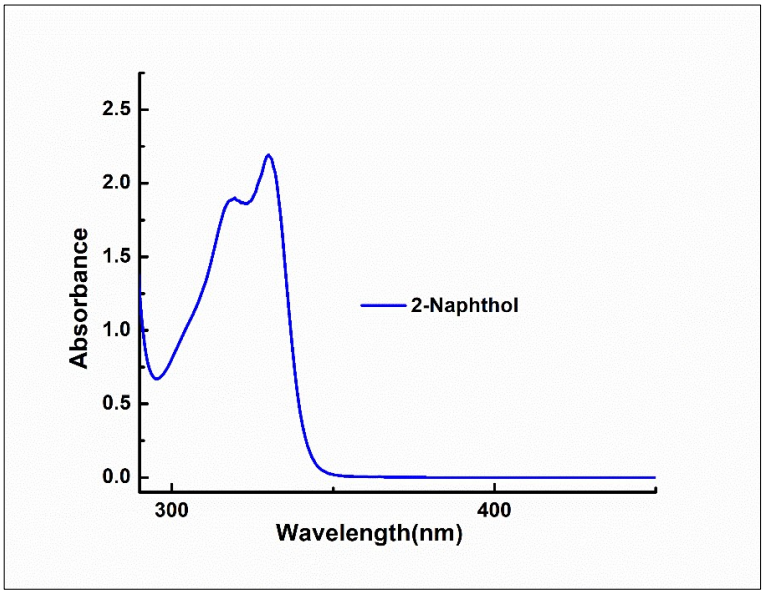


Figure 5.6 UV spectrum of 2-Naphthol (*β*-Naphthol) in methanol (Conc. 1.75 x 10^{-4} mol/L)

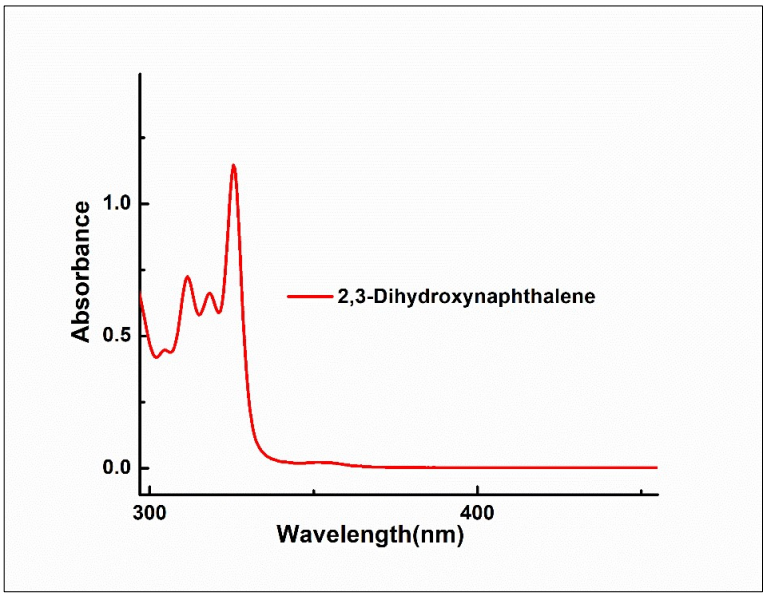


Figure 5.7 UV spectrum of 2,3-Dihydroxynaphthalene in methanol (Conc. 1.0 x 10^{-4} mol/L)

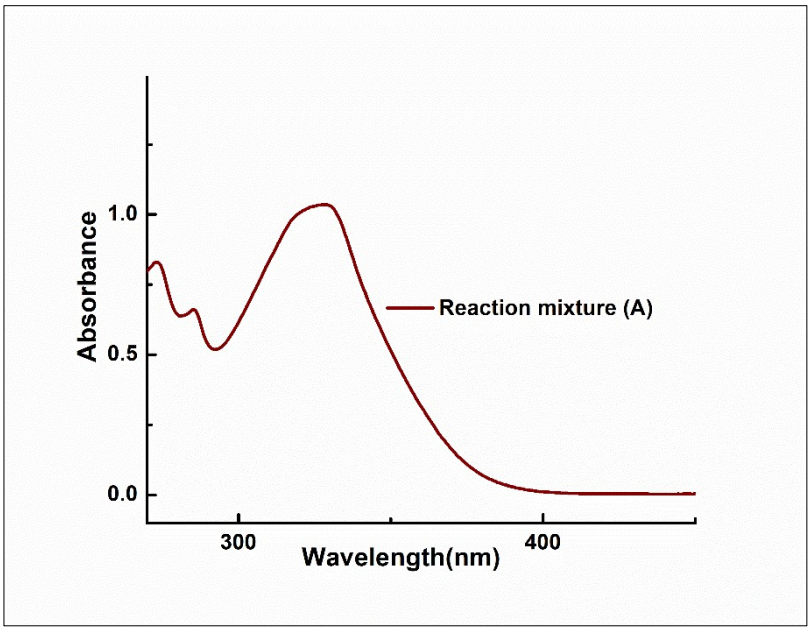


Figure 5.8 UV spectrum of reaction mixture (benzaldehyde, barbituric acid and *β*-naphthol) in methanol (Conc. 2.0 x 10^{-5}mol/L)

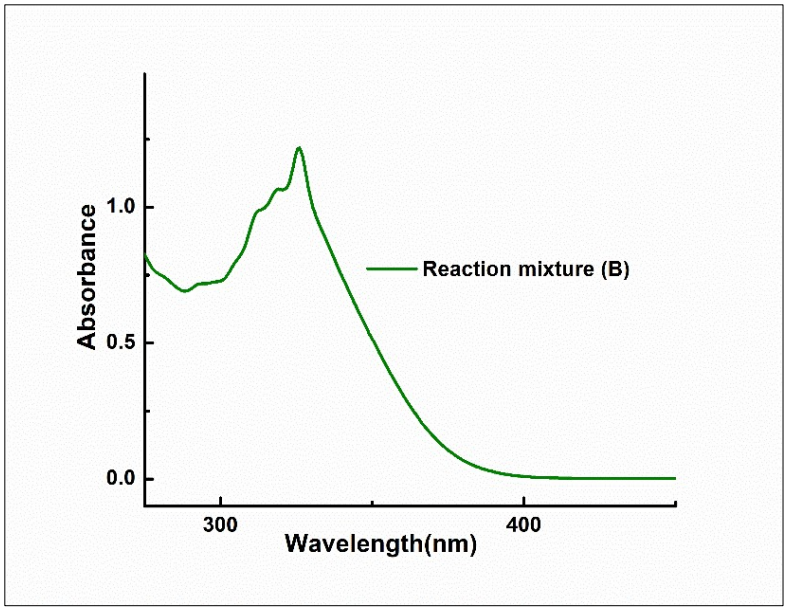


Figure 5.9 UV spectrum of reaction mixture (benzaldehyde, barbituric acid and 2,3-dihydroxynaphthalene) in methanol (Conc. 2.25 x 10^{-5}mol/L)

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