CHAPTER 3

GRINDING INDUCED CATALYST FREE, MULTICOMPONENT SYNTHESIS OF INDOLOINDOLE PYRIMIDINE

Grinding induced catalyst-free, multicomponent synthesis of indoloindole pyrimidine

3.1 Introduction

Multicomponent reactions have risen as a successful and incredible tool in current synthetic organic chemistry, because of their esteemed properties, multicomponent reactions have risen as a successful and incredible tool in current synthetic organic chemistry. Multicomponent reactions give rise to fascinating heterocyclic scaffolds and are advantageous for developing several ‘‘drug-like” molecules [1, 2].

Indole is one of the most essential and abundant nitrogen-containing heterocycles in natural and medicinal products [3]. Compounds having an indole unit show a wide range of biological activities, including antiviral [4], antitumor [5], anticonvulsant [6], anti-inflammatory [7, 8], anti-bacterial [9], and cardiovascular activities [10] .

Pyrimidine and its derivatives play a significant role in numerous pharmacological and biological activities, such as antibacterial, anticonvulsant, antiviral, antifungal, and anticancer properties [11, 12]. They are also a fundamental part of nucleic acid RNA and DNA [13]. Derivatives of pyrimidine have been utilized to produce metal-cage complexes in coordination chemistry and function as CDK 4 inhibitors [14]. Substituted pyrimidines are usually found in naturally occurring and biologically active compounds like avitriptan and voriconazole [15]. Furthermore, the substitution of the indole with an extra heterocyclic ring-

like pyrimidine [16], imidazole [17], oxadiazine pyridine [18], oxazole [19], pyrazole [20], and dihydroimidazole, produced a variety of biologically active compounds. Considering the resourceful pharmaceutical properties of indole and pyrimidine moieties and enhancing indole's biological and pharmacological activity, we synthetically attached the pyrimidine moiety to obtain potent molecules with better biological activity. Some examples containing indole moieties are given below **(Figure. 3.1)**.

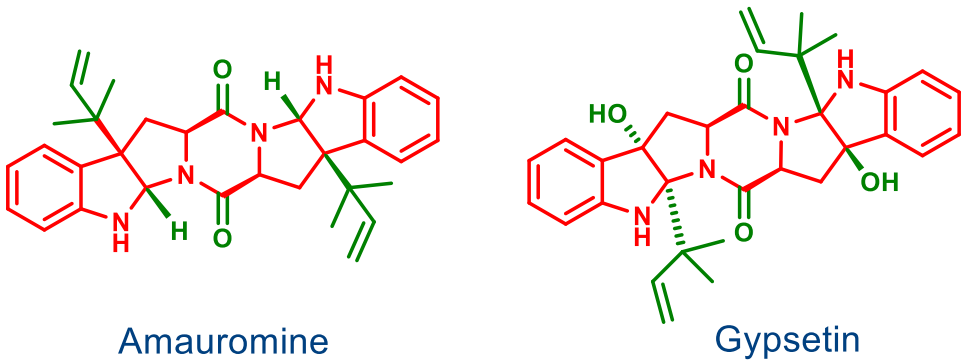
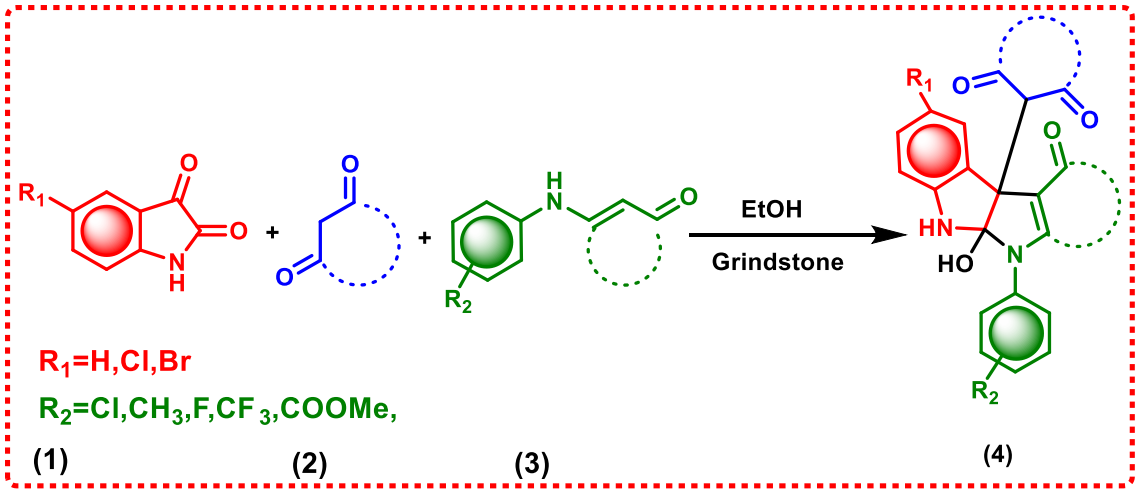


Figure 3.1 Few natural products having indole moieties.

Due to its fascinating biological properties, several methodologies have been developed for the construction of indoloindolpyrimidine derivatives [21]. Nevertheless, many of these approaches have shortcomings, such as harsh reaction conditions, restricted accessibility of starting materials, and the use of costly metal catalysts. Therefore, developing effective and new methods for synthesizing indoloindolpyrimidine derivatives by easily accessible starting materials is of great significance. Enaminones are versatile and powerful building blocks that have been extensively used in synthesizing a variety of biologically active heterocycles [22].

Simple grinding methods using mortar and pestle have taken a central place as a highly valuable approach with the advantages of a simple experimental setup, energy-efficient, economical, and ecologically favorable procedure, and the accessible complexity of the very large number of compounds [23, 24].

In view of the above and as a part of our ongoing research on the synthesis of biologically active heterocyclic compounds [25-27], we report herein an efficient and new protocol for the synthesis of indoloindolpyrimidine derivatives through a one-pot, multicomponent reaction of isatin derivatives (**1**), 1,3 diketones (**2**) and enaminones (**3**) under the grinding condition for 2 h with excellent yield **(86–93% yields, Scheme 3.1)**.

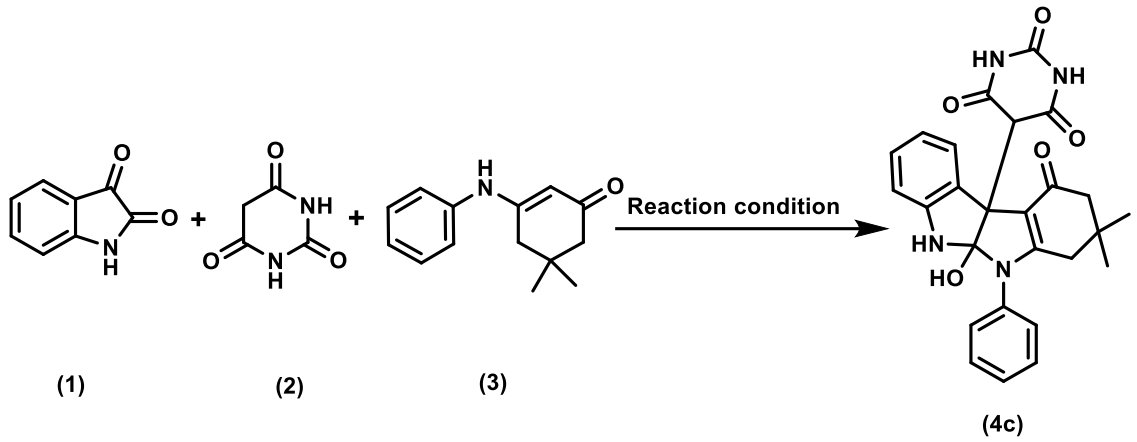


Scheme 3.1 Synthesis of indoloindole pyrimidine derivatives

3.2 Results and Discussion

We have commenced our study to optimize the reaction condition for the preparation of indoloindole pyrimidine via grindstone methodology using isatin (**1**), barbituric acid (**2**), and enaminone (**3)** as a model reaction. Initially, the model reaction was carried out without solvent and catalyst, but it was observed (using TLC) that the reaction did not proceed. A similar reaction was carried out in a few drops of EtOH at room temperature with various catalysts like *p*-TSA, sulfamic acid, L-proline, $Sc(OTf)_3$, CuCl, Et_3N, t-BuOK (**Table 3.1, Entries 2–8**) the reaction proceeds satisfactorily. Further, the same reaction was carried out in different solvents like aprotic and protic, i.e., DMF, DMSO, acetone, toluene, CH_3CN, H_2O, and the molar ratio of EtOH : H_2O at room temperature without the addition of any catalyst, the expected product was observed with low yield (**Table 3.1, Entries 9–18**). Amazingly, when the reaction was carried out in 2–4 drops (approximately 0.2 ml) of ethanol at room temperature without any catalyst, an excellent yield of product (93%) was obtained within 2h (**Table 3.1, Entry 19**). Our methodology has the advantage not only of a higher yield but also of the shortest reaction time. This procedure was best because the liquid-assisted grinding method is better than the dry grinding methodology.

Table 3.1 Optimization condition for the model reaction **4c**[a].



Entry	Catalyst (mol%)	Solvent(drop)	Time(h)	Yields[b] (%)
1.	-	-	6	-
2.	p-TSA (10%)	EtOH	3	80
3.	Sulfamic acid (10%)	EtOH	3	82
4.	L-proline (10%)	EtOH	5	16
5.	$Sc(OTf)_3$ (10%)	EtOH	3	33
6.	CuCl (10%)	EtOH	3	27
7.	Et_3N (10%)	EtOH	4	78

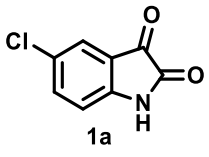
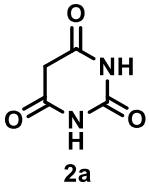
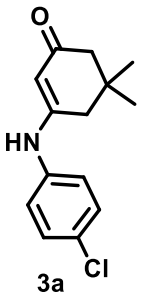
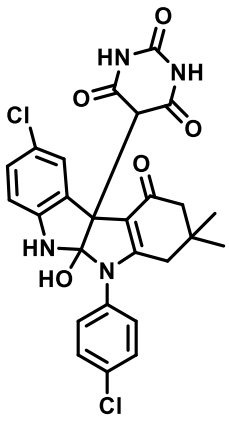
8.	t-BuOK (10%)	EtOH	3	10
9.	None	DMF	3	-
10.	None	DMSO	6	-
11.	None	Acetone	2	-
12.	None	Toluene	5	-
13.	None	CH_3CN	4	75
14.	None	H_2O	6	-
15.	None	EtOH:H_2O (1:1)	3	-
16.	None	2:1	3	10
17.	None	5:1	3	20
18.	None	8:1	3	50
19.	**None**	**EtOH**	**2**	**93**

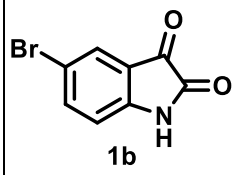
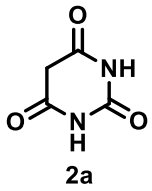
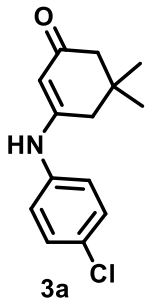
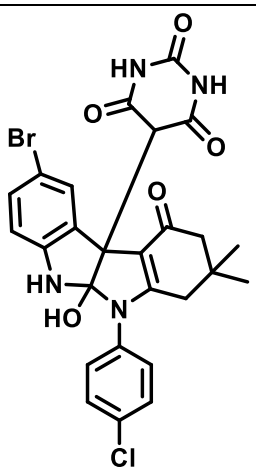
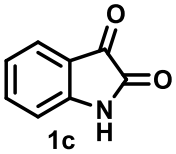
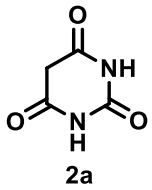
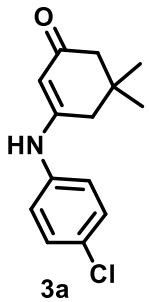
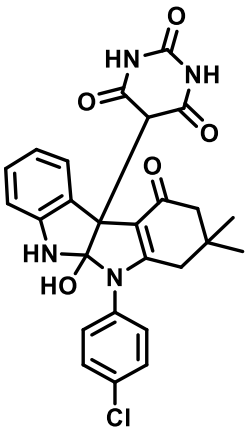
[a]Reaction condition: Isatin(1mmol), barbituric acid (1mmol),and enaminone (1mmol), under grinding.
[b]Isolated yield after recrystallization.

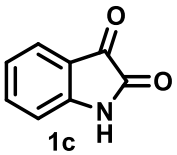
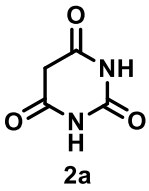
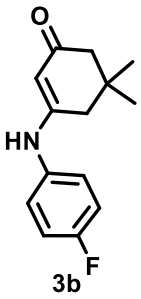
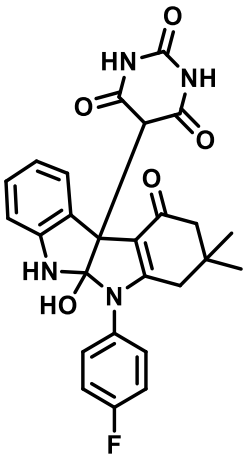
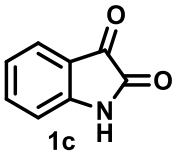
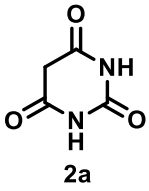
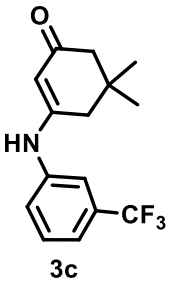
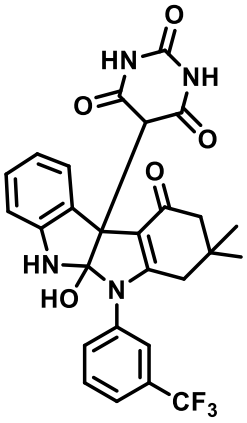
In order to extend the scope of this methodology, a wide range of isatins such as 5-chloro Isatin (**1a**),5-bromo Isatin (**1b**), Isatin (**1c**), barbituric acid (**2a**), and enaminone such as 3-((4-chlorophenyl)amino)-5,5-dimethylcyclohex-2-en-1-one (**3a**), 3-((4-fluorophenyl)am-

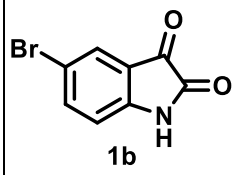
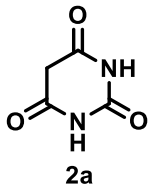
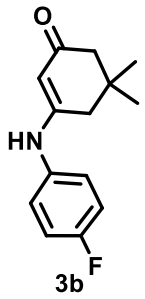
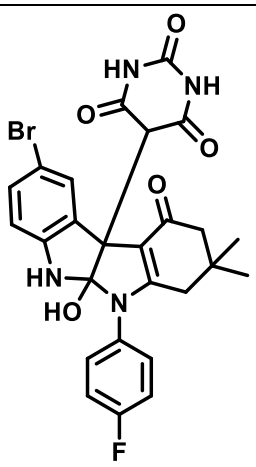
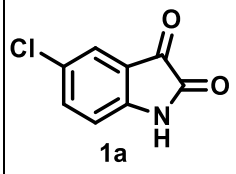
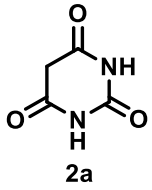
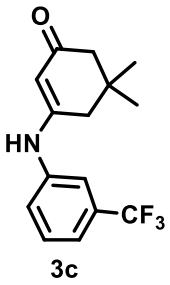
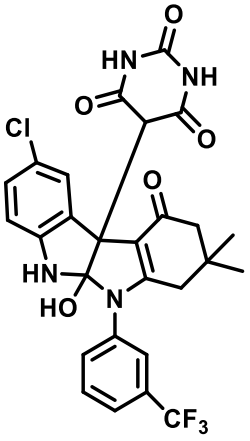
ino)-5,5-dimethylcyclohex-2-en-1-one (**3b**),5,5-dimethyl-3-(((trifluoromethyl)phenyl)a-mino)cyclohex-2-en-1-one (**3c**),methyl4-((5,5-dimethyl-3-oxocyclohex-1-en-1-yl)amin-o)benzoate (**3d**), 5,5-dimethyl-3-(p-tolylamino)cyclohex-2-en-1-one (**3e**) were investi-gated under optimal conditions to afford the product in excellent yield (86-93%, **Table 3.2**).

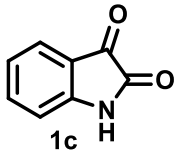
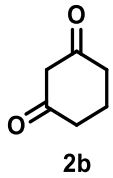
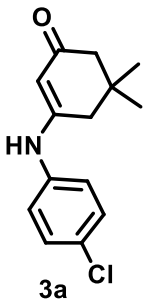
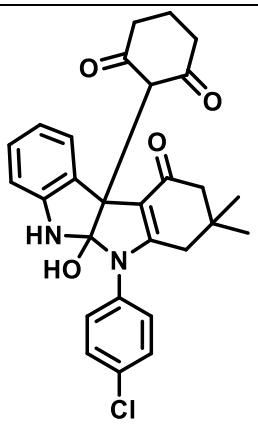
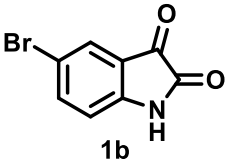
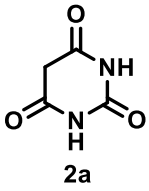
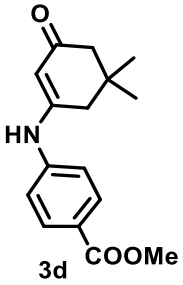
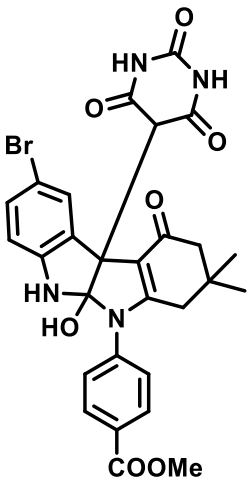
Table 3.2 Investigation of substrate scope for the synthesis of Indoloindole pyrimidine[a]

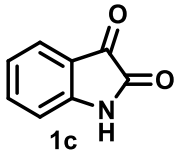
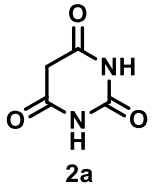
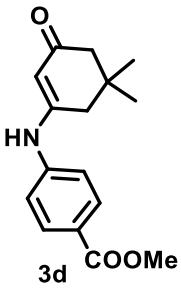
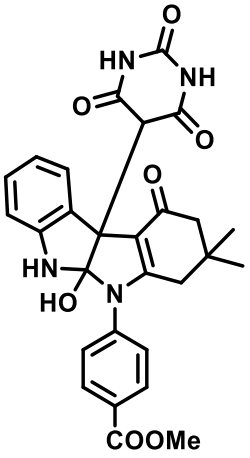
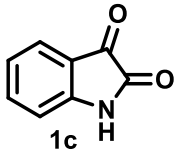
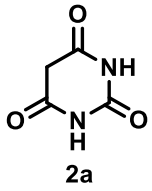
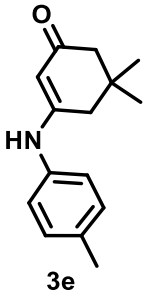
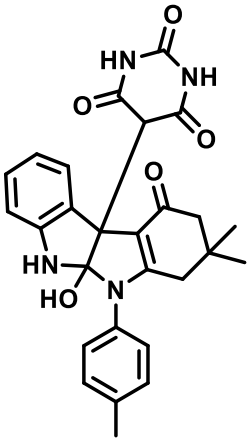
Entry	1	2	3	4[a]	Yield[b](%)
4a	 1a	 2a	 3a		88

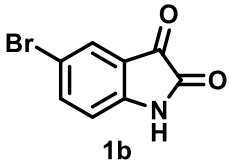
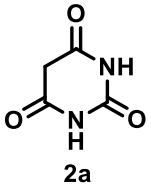
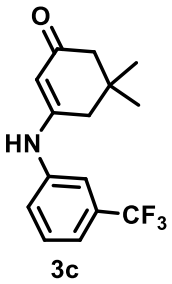
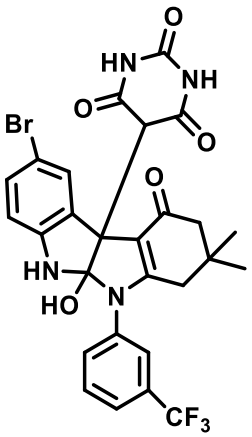
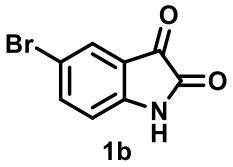
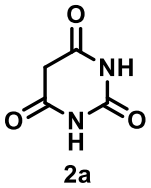
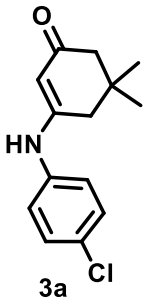
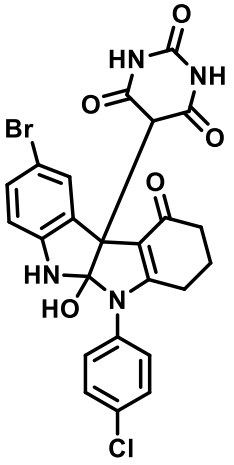
4b	 1b	 2a	 3a		93
4c	 1c	 2a	 3a		91

4d	 1c	 2a	 3b		90
4e	 1c	 2a	 3c		90

4f	 1b	 2a	 3b		91
4g	 1a	 2a	 3c		87

4h	 1c	 2b	 3a		86
4i	 1b	 2a	 3d		91

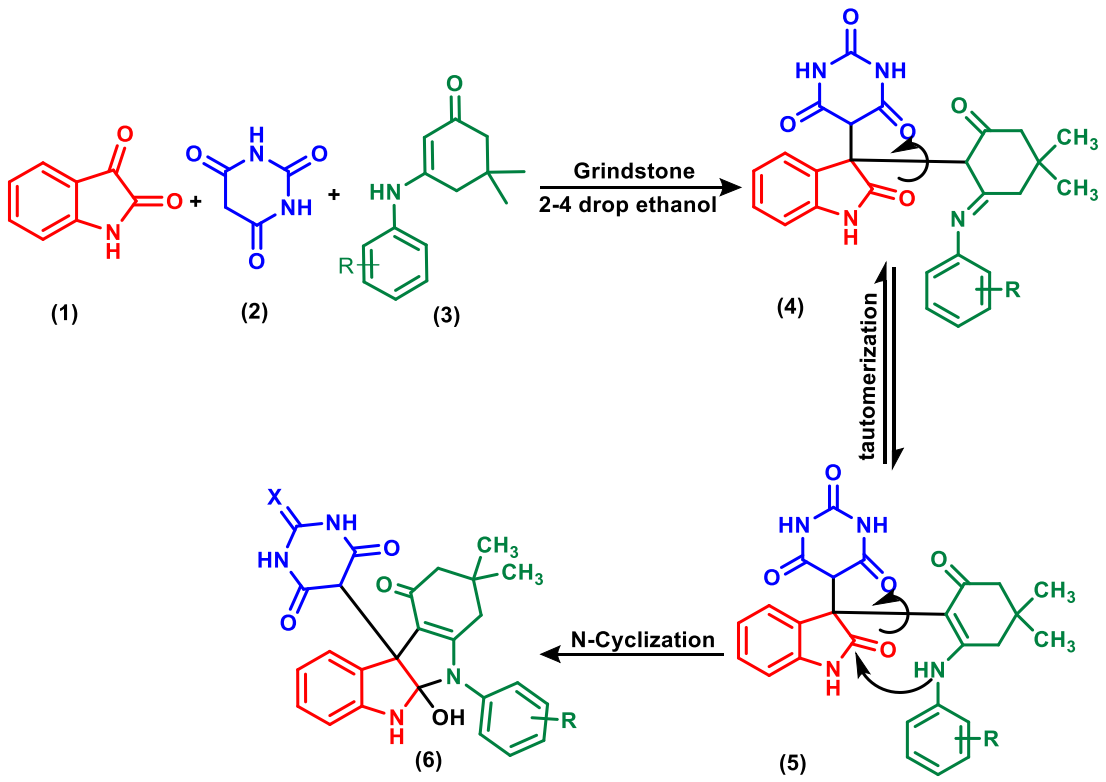
4j	 1c	 2a	 3d		92
4k	 1c	 2a	 3e		86

4l	 1b	 2a	 3c		89
4m	 1b	 2a	 3a		87

[a]Reaction condition: Isatin(1mmol), barbituric acid (1mmol),and enaminone (1mmol), under grinding.
[b]Isolated yield after recrystallization.

A suitable reaction mechanism is proposed based on product isolation and represented in **Scheme 3.2**. Initially, the Knoevenagel adduct is formed by the reaction of barbituric acid and isatin; after then, a Michael-type addition takes place via enamine and gives an open-chain intermediate. This intermediate undergoes imineenamine tautomerization and N-

cyclization via the attack to the carbonyl group of amidic isatin produces **6 (Scheme 3.2)**.



Scheme 3.2 Plausible reaction mechanism

3.3 Conclusion

In conclusion, the present article describes the catalyst-free multicomponent synthesis of indoloindole pyrimidine via grinding methodology in a few drops of ethanol. This current approach offers some distinctive benefits such as eco-friendly, green protocol, short reaction times, good yields, and simple workup.

3.4 Experimental section

3.4.1 General experimental procedure for the synthesis of compound (4)

In this procedure, a mixture of isatin (1 mmol), enaminone (1 mmol), and diketone (1 mmol) was grinded in a specific size of mortar and pestle in the presence of a few drops (2–4 drops or 0.2 ml) of ethanol (3.43 mmol). The progress of the reaction was monitored by thin-layer chromatography (ethyl acetate: hexane 6:4). After the completion of the reaction, the product was recrystallized with hot ethanol to give the desired product in good yield.

3.4.2 Analytical data

5-(9-Chloro-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4a)

Cream powder, yield 88%, m. p. 218 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.61 (s, 1H), 10.42 (s, 1H), 10.09 (s, 1H), 7.95 (d, 1H), 7.68-7.63 (m, 3H), 7.60-7.59 (m, 1H), 7.48 (m, 1H), 7.32(m, 2H), 5.97 (s, 1H), 3.34 (br,1H), 3.07 (d, 2H), 3.04 – 2.90 (m, 2H), 1.13 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 165.24, 160.68, 150.09, 149.25, 144.25, 137.95, 134.79, 131.19, 130.83, 129.65, 128.94, 127.68, 125.98, 125.45, 124.63, 123.85, 121.51, 90.64, 47.27, 40.56, 40.47, 40.39, 40.30, 40.23, 40.13, 39.97, 39.80, 39.63, 39.47, 33.04, 28.12. ; **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3725, 3414 (OH, NH), 2936 (CH), 1667, 1564 (C=O), 1251 (C-O), 763 (Ar). **Anal. Calc. for $C_{26}H_{22}Cl_2N_4O_5$:** C, 57.68; H, 4.10; N, 10.35. Found C,

57.75; H, 4.32; N, 10.61. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{22}Cl_2N_4O_5$, 541.3850; found, 541.3846.

5-(9-Bromo-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4b)

Cream powder, yield 93%, m. p. 221 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.60 (s, 1H), 10.42 (s, 1H), 10.09 (s, 1H), 7.91 (d, 1H), 7.80 (d, 1H), 7.65 – 7.62 (m, 3H), 7.33 (d, 2H), 5.97 (s, 1H), 3.34 (br,1H)3.01 (d, 4H), 1.13 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 165.24, 160.79, 151.57, 149.28, 144.43, 137.94, 134.66, 132.23, 130.94, 128.95, 127.73, 127.07, 126.50, 125.42, 124.61, 121.51, 119.72, 91.09, 47.30, 40.48, 40.40, 40.31, 40.23, 40.14, 39.98, 39.81, 39.64, 39.47, 33.02, 28.10. **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3745, 3423 (OH, NH), 2946 (CH), 1657, 1565 (C=O), 1257 (C-O), 767 (Ar). **Anal. Calc. for $C_{26}H_{22}BrClN_4O_5$:** C, 53.31; H, 3.79; N, 9.56. Found C, 53.52; H, 3.91; N, 9.86. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{22}BrClN_4O_5$, 585.8390; found 585.8386.

5-(5-(4-Chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4c)

Cream powder, yield 91%, m. p. 216 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.58 (s, 1H), 10.37 (s, 1H), 10.06 (s, 1H), 7.94 (d, 1H), 7.70 – 7.64 (m, 3H), 7.60 (m, 1H), 7.50 (m, 1H), 7.36 – 7.27 (m, 2H), 5.92 (s, 1H), 3.33 (br,1H), 3.06-3.09 (d, 2H), 2.96-2.99 (d, 2H), 1.14 (s,

6H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 165.87, 159.81, 150.10, 148.30, 145.75, 138.18, 135.80, 129.27, 128.81, 128.53, 127.43, 126.89, 125.45, 125.07, 124.83, 124.38, 121.51, 90.75, 47.38, 40.57, 40.48, 40.40, 40.31, 40.24, 40.15, 40.07, 39.98, 39.81, 39.64, 39.48, 33.00, 28.0 . **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3727, 3417 (OH, NH), 2933 (CH), 1667, 1562 (C=O), 1251 (C-O), 765 (Ar). **Anal. Calc. for $C_{26}H_{23}ClN_4O_5$:** C, 61.60; H, 4.57; N, 11.05. Found C, 62.25; H, 4.83; N, 10.78. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{23}ClN_4O_5$, 506.9430; found, 506.9424.

5-(5-(4-Fluorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4d)

Cream powder, yield 90%, m. p. 230 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.56 (s, 1H), 10.27 (s, 1H), 10.05 (s, 1H), 7.94 (d, 1H), 7.68 – 7.59 (m, 4H), 7.51 – 7.47 (m, 1H), 7.09 (t, 2H), 5.92 (s, 1H), 3.33 (br,1H), 3.20 – 2.88 (m, 4H), 1.14 (s, 6H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 165.62, 159.79, 159.50, 157.60, 150.10, 148.18, 145.81, 135.95, 135.67, 129.23, 128.52, 126.83, 125.52, 125.15, 124.94, 124.35, 121.70, 121.64, 115.54, 115.36, 90.90, 47.43, 40.58, 40.49, 40.42, 40.33, 40.25, 40.16, 40.08, 39.99, 39.82, 39.66, 39.49, 32.99, 28.10. **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3735, 3453 (OH, NH), 2961 (CH), 1696, 1595 (C=O), 1236 (C-O), 773 (Ar). **Anal. Calc. for $C_{26}H_{23}FN_4O_5$:** C, 63.67; H, 4.73; N, 11.42. Found C, 63.92; H, 4.67; N, 11.67. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{23}FN_4O_5$, 490.4914; found, 490.4910.

5-(5a-Hydroxy-3,3-dimethyl-1-oxo-5-(3-(trifluoromethyl)phenyl)-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4e)

Cream powder, yield 90%, m. p. 216 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.56 (d, 2H), 10.01 (s, 1H), 8.07 (s, 1H), 7.96 (d, 1H), 7.85 (d, 1H), 7.67 (t, 1H), 7.60 (d, 1H), 7.51 (q, 2H), 7.41 (d,1H), 5.94 (s, 1H), 3.34 (br,1H), 3.20 – 2.87 (m, 4H), 1.14 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 166.28, 159.83, 157.18, 150.00, 148.41, 145.81, 144.01, 139.95, 135.54, 130.13, 129.66, 129.30, 128.57, 126.99, 125.40, 124.99, 124.77, 124.45, 123.43, 122.85, 120.33, 115.99, 90.84, 47.37, 43.53, 40.49, 40.32, 40.24, 40.15, 39.99, 39.82, 39.65, 39.49, 37.36, 33.01, 28.23. **IR (KBr) ($\bar{\upsilon}_{max}$/cm^{-1}):** 3457, 3429, 3062 (OH, NH), CH (2892), 1672, 1582 (C=O), 1266 (C-O); 756 (Ar). **Anal. Calc. for $C_{27}H_{23}F_3N_4O_5$:** C, 60.00; H, 4.29; N, 10.37. Found C, 60.12; H, 4.41; N, 10.67. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{23}F_3N_4O_5$, 540.4992; found, 540.4987.

5-(9-Bromo-5-(4-fluorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4f)

Cream powder, yield 91%, m. p. 220 ˚C, **^{1}H NMR (500 MHz, DMSO-d^{6}) δ** 10.59 (s, 1H), 10.33 (s, 1H), 10.07 (s, 1H), 7.91 (d, 1H), 7.80 (d, 1H), 7.72 – 7.59 (m, 3H), 7.39 (s, 1H), 7.11 (t, 2H), 5.97 (s, 1H), 3.33 (br, 1H), 3.22 – 2.81 (m, 4H), 1.13 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^{6}) δ** 164.99, 160.78, 150.07, 144.44, 136.10, 134.82, 132.19, 130.93, 119.67, 115.70, 115.52, 90.76, 47.32, 40.49, 40.42, 40.33, 40.25, 40.16, 40.09, 39.83, 39.66, 39.49,

33.01, 28.08, 23.27. **IR (KBr) ($\tilde{\upsilon}_{max}$/cm^{-1}):** 3459, 3096 (OH, NH), 2972 (CH), 1632, 1563 (C=O)**,** 1195(C-O). **Anal. Calc. for $C_{26}H_{22}BrFN_4O_5$:** C, 54.85; H, 3.89; N, 9.84. Found C, 54.96; H, 3.78; N, 9.77. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{26}H_{22}BrFN_4O_5$, 569.3874; found, 569.3872.

5-(9-Chloro-5a-hydroxy-3,3-dimethyl-1-oxo-5-(3-(trifluoromethyl)phenyl)-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4g)

Cream powder, yield 87%, m. p. 216 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.59 (s, 2H), 10.02 (s, 1H), 8.05 – 7.88 (m, 2H), 7.84 (d, 1H), 7.71 (d, 1H), 7.51 (m, 2H), 7.43 (d, 1H), 5.99 (s, 1H), 3.35 (br, 1H), 3.03 (d, 4H), 1.14 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 165.64, 160.72, 149.96, 144.27, 139.72, 134.54, 131.29, 130.87, 130.26, 129.71, 125.89, 125.54, 123.76, 123.42, 90.58, 47.24, 40.49, 40.41, 40.32, 40.25, 40.15, 39.98, 39.82, 39.65, 39.48, 34.42, 33.05, 22.77, 15.30. **Anal. Calc. for $C_{27}H_{22}ClF_3N_4O_5$:** C, 56.41; H, 3.86; N, 9.74. Found C, 56.66; H, 3.71; N, 9.93. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{27}H_{22}ClF_3N_4O_5$, 574.9412; found, 574.9408.

2-(5-(4-Chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)cyclohexane-1,3-dione(4h)

Cream powder, yield 86%, m. p. 241 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.98 (s, 1H), 7.32 (s, 1H), 7.12– 7.08 (m, 1H), 7.01 – 6.96 (m, 2H), 6.85-6.79 (m, 3H), 6.69 – 6.66 (m, 1H), 3.99 (s, 1H), 3.34 (br, 1H), 2.45 – 2.41 (m, 1H), 2.19 – 2.05 (m, 8H), 1.87 – 1.69 (m,

7H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 204.30, 194.79, 182.46, 170.49, 144.85, 133.77, 127.89, 121.88, 121.80, 112.97, 109.70, 100.98, 59.63, 47.13, 40.82, 40.60, 40.51, 40.44, 40.35, 40.27, 40.18, 40.11, 40.01, 39.85, 39.68, 39.51, 37.23, 35.67, 29.55, 20.58, 20.07. **Anal. Calc. for $C_{27}H_{26}ClN_2O_4$:** C, 67.85; H, 5.48; N, 5.86. Found C, 67.69; H, 5.62; N, 5.51. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{27}ClN_2O_4$, 490.9840; found, 490.9835.

Methyl-4-(9-bromo-5a-hydroxy-3,3-dimethyl-1-oxo-10b(2,4,6-trioxohexahydro-pyrimid-in-5-yl)-2,3,4,5a,6,10b-hexahydro-1H-indolo[2,3-b]indol-5-yl)benzoate(4i)

Cream powder, yield 91%, m. p. 232 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.62 (d, 2H), 9.99 (s, 1H), 7.91 (t, 3H), 7.81 (d, 1H), 7.73 (d, 2H), 7.67 (s, 1H), 5.98 (s, 1H), 3.85 (s, 3H), 3.41 (br, 1H), 2.95 (s, 4H), 1.14 (s, 6H). **^{13}C NMR (126 MHz, DMSO-d^6) δ** 166.39, 165.71, 160.80, 150.02, 149.40, 144.44, 143.31, 134.48, 132.27, 130.97, 130.58, 127.00, 126.42, 125.48, 124.80, 124.54, 119.78, 119.44, 58.84, 52.35, 51.11, 47.28, 42.03, 40.50, 40.33, 40.17, 40.00, 39.83, 39.67, 39.50, 34.36, 33.04, 31.72, 28.13, 26.41, 19.02. **Anal. Calc. for $C_{28}H_{25}BrN_4O_7$:** C, 55.18; H, 4.13; N, 9.19. Found C, 55.73; H, 4.33; N, 9.31. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{25}BrN_4O_7$, 609.4330; found, 609.4327.

Methyl 4-(5a-hydroxy-3,3-dimethyl-1-oxo-10b-(2,4,6-trioxohexahydropyrimidin-5-yl)-2,3,4,5a,6,10b-hexahydro-1H-indolo[2,3-b]indol-5-yl)benzoate(4j)

Cream powder, yield 92%, m. p. 228 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 11.11 (s, 1H), 10.58 (d, 1H), 9.96 (s, 1H), 7.95 (d, 1H), 7.88 (d, 2H), 7.75 (d, 2H), 7.70 – 7.63 (m, 1H), 7.61

(d, 1H), 7.57 – 7.47 (m, 1H), 5.92 (s, 1H), 3.85 (s, 3H), 3.36 (br, 1H), 3.03 (m, 4H), 1.14 (s, 6H).**^{13}C NMR (126 MHz, DMSO-d^6) δ** 166.43, 159.82, 151.19, 150.05, 147.77, 145.81, 143.58, 135.59, 130.47, 129.29, 128.57, 127.85, 126.94, 125.40, 124.98, 124.55, 119.41, 52.32, 47.39, 43.93, 40.49, 40.42, 40.33, 40.25, 40.16, 39.99, 39.83, 39.66, 39.49, 33.02, 28.14. **Anal. Calc. for $C_{28}H_{26}N_4O_7$:** C, 63.39; H, 4.49; N, 10.56. Found C, 63.68; H, 4.32; N, 10.41. **HRMS** (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{28}H_{26}N_4O_7$, 530.5370; found, 530.5368.

5-(5a-Hydroxy-3,3-dimethyl-1-oxo-5-(p-tolyl)-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4k)

Cream powder, yield 86%, m. p. 219 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.56 (d, 1H), 10.12 (s, 2H), 8.10 – 6.80 (m, 8H), 5.97 (s, 1H), 3.33 (br, 1H), 3.02 (d, 3H), 2.43 – 2.06 (m, 4H), 1.13 (s, 6H). **Anal. Calc. for $C_{26}H_{25}N_4O_5$:** C, 65.95; H, 5.32; N, 11.83. Found C, 65.61; H, 5.12; N, 11.41.

5-(9-Bromo-5a-hydroxy-3,3-dimethyl-1-oxo-5-(3-(trifluoromethyl)phenyl)-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione(4l)

Cream powder, yield 89%, m. p. 226 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 10.59 (s, 2H), 10.01 (s, 1H), 8.09 – 7.35 (m, 7H), 5.98 (s, 1H), 3.38 (br, 1H), 3.02 (d, 4H), 1.13 (s, 6H). **Anal. Calc. for $C_{27}H_{22}BrF_3N_4O_5$:** C, 52.36; H, 3.58; N, 9.05. Found C, 52.92; H, 3.21; N, 9.47.

5-(9-Bromo-5-(4-chlorophenyl)-5a-hydroxy-1-oxo-1,3,4,5,5a,6-hexahydro-2H-indolo[2,3-b]indol-10b-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4m)

Cream powder, yield 87%, m. p. 218 ˚C, **^{1}H NMR (500 MHz, DMSO-d^6) δ** 11.63 (s, 1H), 11.06 (s, 1H), 10.67 (s, 1H), 9.33 – 8.68 (m, 2H), 8.45 – 7.88 (m, 2H), 7.87 – 7.35 (m, 3H), 7.00 (m, 1H), 5.56 (s, 1H), 3.35 (br, 1H), 3.06 (s, 4H), 2.23 (d, 2H). **Anal. Calc. for $C_{24}H_{18}BrClN_4O_5$:** C, 51.68; H, 3.25; N, 10.04. Found C, 51.92; H, 3.23; N, 10.47.

3.4.3 Spectral Data of Product 5-(9-chloro-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydroindolo[2,3-b]indol-10b(2H)-yl)pyrimidine-2,4,6(1H,3H,5H)-trione (4a)

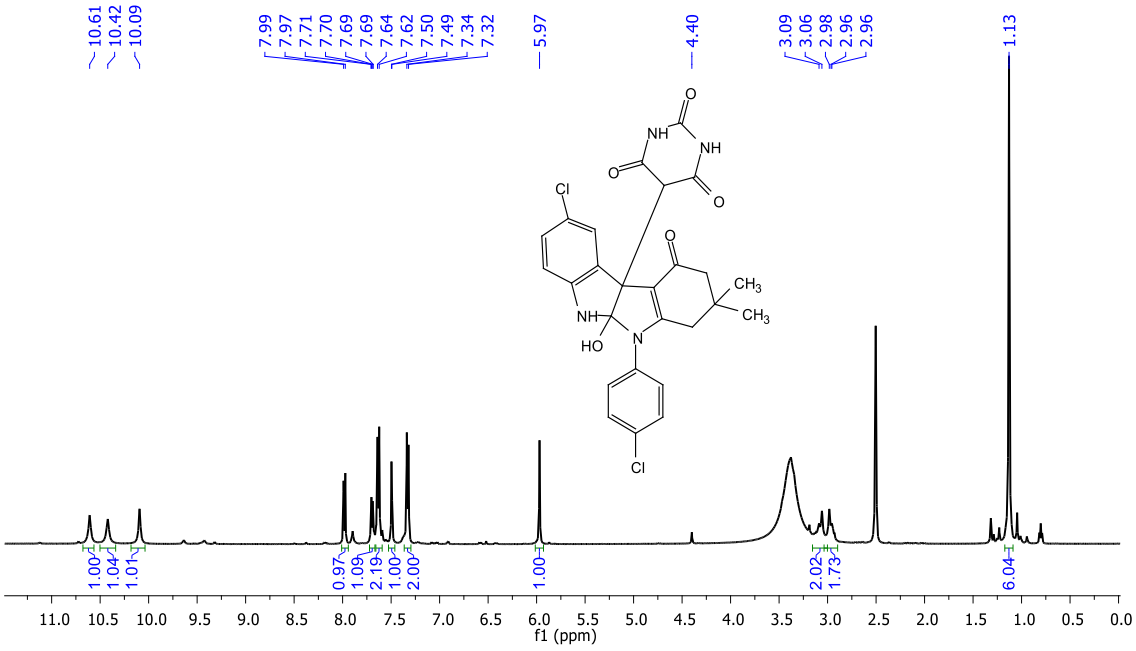


Figure 3.2 ^{1}H NMR of 5-(9-chloro-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydroindolo[2,3-b]indol-10b(2H)-yl)pyrimidine-2,4,6(1H,3H,5H)-trione **(4a)**

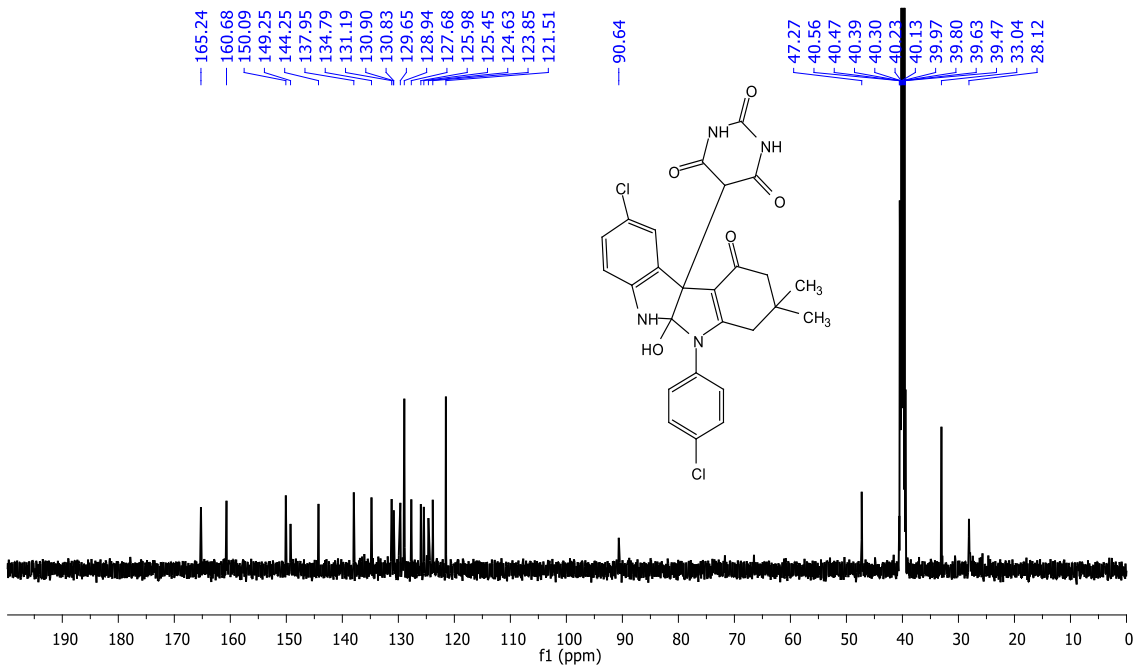


Figure 3.3 ^{13}C NMR of 5-(9-chloro-5-(4-chlorophenyl)-5a-hydroxy-3,3-dimethyl-1-oxo-1,3,4,5,5a,6-hexahydroindolo[2,3-b]indol-10b(2H)-yl)pyrimidine-2,4,6(1H,3H,5H)-trione **(4a)**

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