4.1 Introduction

In the last two decades, mechanochemistry, or chemical transformations involving mechanical energy, has exploded in popularity.[1,2] They are one of the top ten world-changing technologies, according to IUPAC.[3] Mechanical energy from shearing, kneading, grinding, or milling aids the transformations.[4] The technique addresses several aspects of Green Chemistry, including a significant reduction in or elimination of solvents, environmental conditions, fast reaction kinetics, and the absence of a lengthy workup step.[5] This bright advancement is a viable alternative to various chemical transformations developed in the solution phase, with frequently higher yields.[6]

Ball milling has been shown to be effective in encouraging chemical reactions by transmitting mechanical force in a variety of chemistry domains.[4,6–11] Most of these methods are solvent-free, indicating that they are more sustainable than their solvent-based alternatives. Mechanochemistry can vary established or trigger novel reactivity/selectivity patterns, which opens up exciting possibilities for organic synthesis.[12–17] Recent studies have shown that a variety of organic reactions, including multicomponent couplings,[18–20] simple organic functionalizations, metal catalysis,[21,22] asymmetric synthesis,[23,24] and the synthesis of heterocycles can be carried out in ball mills.

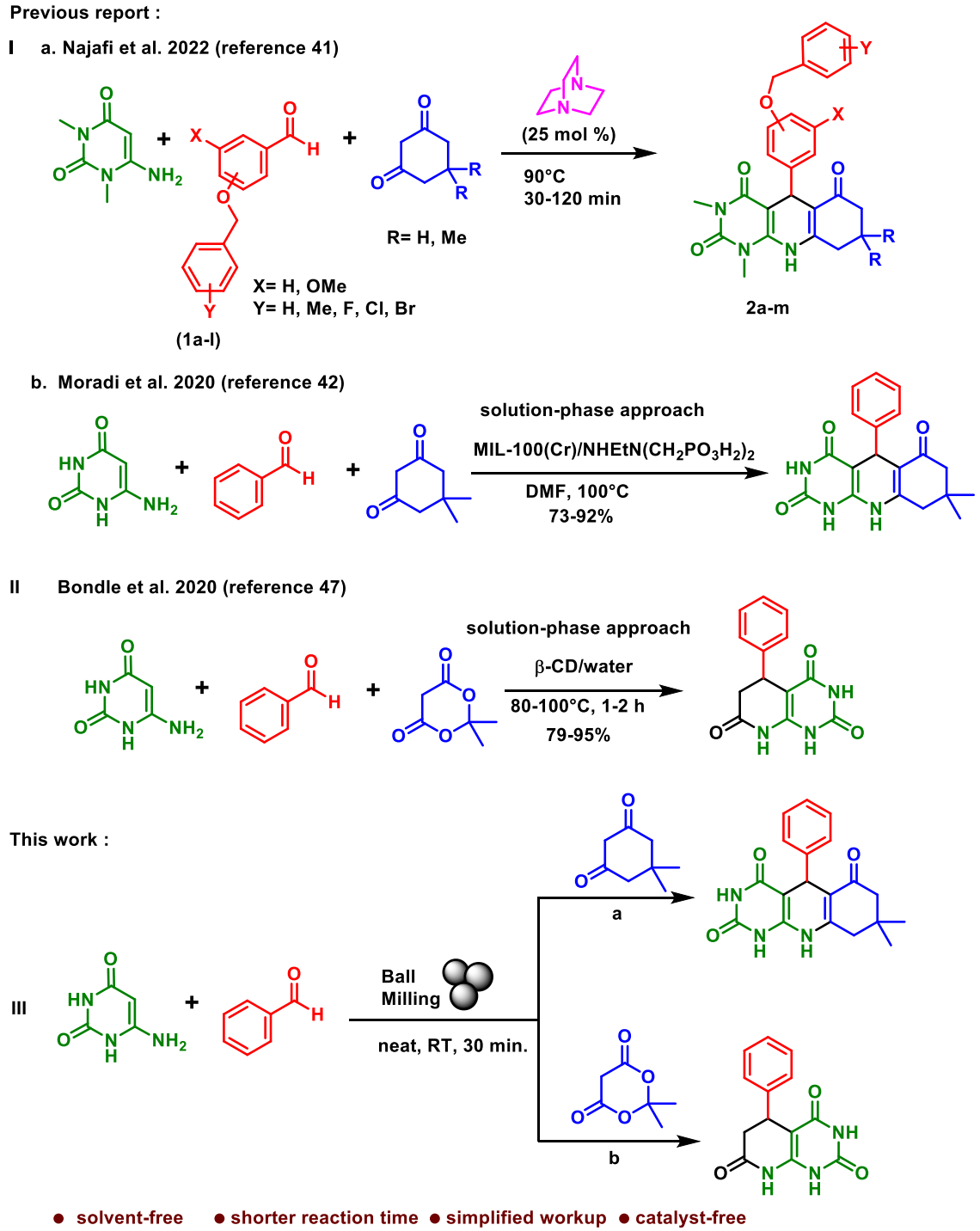
N-Heterocyclic compounds, such as the derivatives of uracil, are one of the most significant categories of compounds in organic synthesis. Pyrimidines and quinoline derivatives with uracil in their structural makeup are notable chemical compounds because of their

pharmacological effectiveness, cardiotonic, antitumor, antihypertensive, hepatoprotective, antifungal, and antibronchitic activity properties.[25–27] Additionally, in general, N-heterocyclic scaffolds have gained more prominence in pharmaceutical and medicinal chemistry among heterocyclic compounds. Due to a wide range of biological activities, Pyrimido [4,5-b] quinolines are an important class of heterocyclic compounds.[28–33] These compounds include amlodipine, felodipine, nicardipine, and nifedipine, which were calcium channel modulators and successfully developed as antihypertensive and cardiovascular drugs.[34–37] Another N-heterocyclic scaffolds, pyrido[2,3-d]pyrimidine, are also important compound with a broad range of biological activities and pharmaceutical profile, such as the anti-HIV agent, the anti-allergic agent ramastine, and the human leukocyte elastase inhibitor SSR69071.[38–40]

Numerous one-pot protocols have been reported due to the significant biological and synthetic importance of pyrimido [4,5-b] quinoline derivatives; however, these protocols either use high temperatures, produce lower yields, or take a longer time to complete. Very recently, Soheila Esmaili and coworkers[41] reported DABCO catalysed synthesis of pyrimido [4,5-b] quinolone, this required a high mol % of catalyst, long reaction time and high temperature. (**Scheme 4.1 (Ia)**) Next, Zarei and coworkers reported the same class of compound[42] using phosphorous acid anchored nanoporous catalyst [MIL-100(Cr)/NHEtN($CH_2PO_3H_2$)$_2$], but this required, high temperature, as well as use of a toxic solvent. (**Scheme 4.1(Ib)**) In comparison, only a few methods for the synthesis of dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,8H)-triones, such as the condensation of

aldehyde, Meldrum's acid, 6-aminouracil in the presence of CAN, HAp-encapsulated-γ-Fe_2O_3[γ-Fe_2O_3@HAp-SO_3H], triethyl benzyl ammonium chloride (TEBAC), and ionic liquid [DMBSI]HSO_4[43–46] have been reported. However, many of these approaches have drawbacks, including lengthy reaction times, low yields, laborious set-up processes that produce significant amounts of waste containing toxic metals, and using costly reagents. A mild catalytic protocol, like using reactions supported by β-cyclodextrin (β-CD), has been reported[47] to get around some of these drawbacks. (**Scheme 4.1 (II)**) They, too, have disadvantages, and even though several methods for producing pyrido[2,3-d]pyrimidine heterocycles are available, no report on the synthesis of such skeletons under mechanochemical, solvent-free, and catalyst-free approaches has been published to date. (**Scheme 4.1**)

As a part of our ongoing research work to develop environmentally friendly methods for organic synthesis,[48–55] herein, we report first time our result for a nearly green synthesis protocol for pyrimido [4,5-b] quinolines and pyrimido [2,3-d] pyrimidines via one-pot multicomponent reaction of aromatic aldehyde, 6-amino uracil, and 1,3-diketo compounds under ball-milling condition within a brief reaction time (**Scheme 4.1 (III a and b)**).



Scheme 4.1 Solution-Phase and Mechanochemical Solvent-free Approaches towards Pyrimido [4,5-b]quinolones and Pyrido [2,3-d] pyrimidines

4.2 Results and Discussion

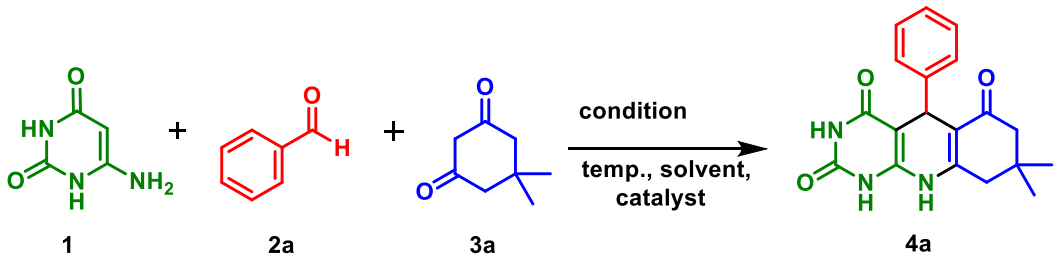
For the Initial test reaction, a mixture of 6-aminouracil (**1a**, 1 mmol), benzaldehyde (**2a**, 1 mmol), and dimedone (**3a**, 1 mmol) was reacted in an aqueous medium with sulfamic acid (10 mol%) at room temperature for 5 hours (Table 4.1, entry 1). We were delighted to find a pure solid Pyrimido [4,5-b] quinolines derivative (**4a**) with a decent yield of 58%. Lower yields were obtained when the same reaction was conducted in an aqueous medium in the presence of various catalysts, including *p*-TSA, L-proline, CF_3COOH, and DBU (31%, 21%, 18%, and 25%, respectively) (Table 4.1, entries 2-5). Next, we observed that in an ethanolic medium, for the same reaction in the presence of sulfamic acid (10 mol%), a lower yield (55%) was obtained (Table 1, entry 6). The desired compound was obtained in low yields with aprotic solvents, such as dichloromethane, tetrahydrofuran, and acetonitrile (Table 4.1, entries 7–9), were used for further analysis. After that, we investigated the temperature effect and refluxed the reaction while maintaining the same catalytic conditions, but no appreciable improvement of the desired product was seen (Table 4.1, entries 10 and 11). In order to carry out the reaction under solvent-free conditions, we focused on the idea that "no solvent is the best solvent" and initially heated the reaction at 120°C (Table 4.1, entry 12). These findings indicated that the yield formation had increased but was not very promising. As a result, we repeated the process of carrying out the reaction by switching from stirring to grinding in a mortar and pestle for 1 hour, and 71% of the desired Pyrimido [4,5-b] quinolines derivative was produced (Table 4.1, entry 13). Next, we turned to carry out the reaction under ball-milling conditions (planetary Ball-milling apparatus PM 100). We have observed that using ten balls (10 mm) with 200 rpm for 2 h gave a good result (82%) (Table 4.1, entry 14). By

increasing the speed of ball milling (rpm) from 200 rpm to 650 rpm, the yield increased to 95%, and reaction time decreased up to 30-35 min (Table 4.1 entries 14-17).

Thus, optimal reaction conditions were obtained using 6-aminouracil (**1a,** 1mmol), benzaldehyde (**2a**, 1 mmol), and dimedone (**3a**, 1mmol) under ball-milling conditions (10 balls with 650 rpm) for 30 min (Table 4.1, entry 17).

A gram-scale reaction (10 mmol scale) was also performed to confirm the reaction's synthetic efficacy. It was discovered that the reaction proceeded smoothly and with the same efficiency, emphasizing the reaction's benefits for synthetics (Table 4.1, entry 18).

Table 4.1 Optimization of the Reaction Conditions[a]



1 2a 3a 4a

entry	catalyst (mol%)	solvent	condition	temperature (°C)	yield[b] (%)
1	Sulfamic acid (10 mol%)	H_2O	stirring	RT	58
2	p-TSA (10 mol%)	H_2O	stirring	RT	31
3	L-proline (10 mol%)	H_2O	stirring	RT	21
4	CF_3COOH	H_2O	stirring	RT	18
5	DBU (10 mol%)	H_2O	stirring	RT	25
6	Sulfamic acid (10 mol%)	ethanol	stirring	RT	55
7	Sulfamic acid (10 mol%)	MeCN	stirring	RT	none
8	Sulfamic acid (10 mol%)	DCM	stirring	RT	none
9	Sulfamic acid (10 mol%)	THF	stirring	RT	none
10	Sulfamic acid (10 mol%)	H_2O	stirring	reflux	65

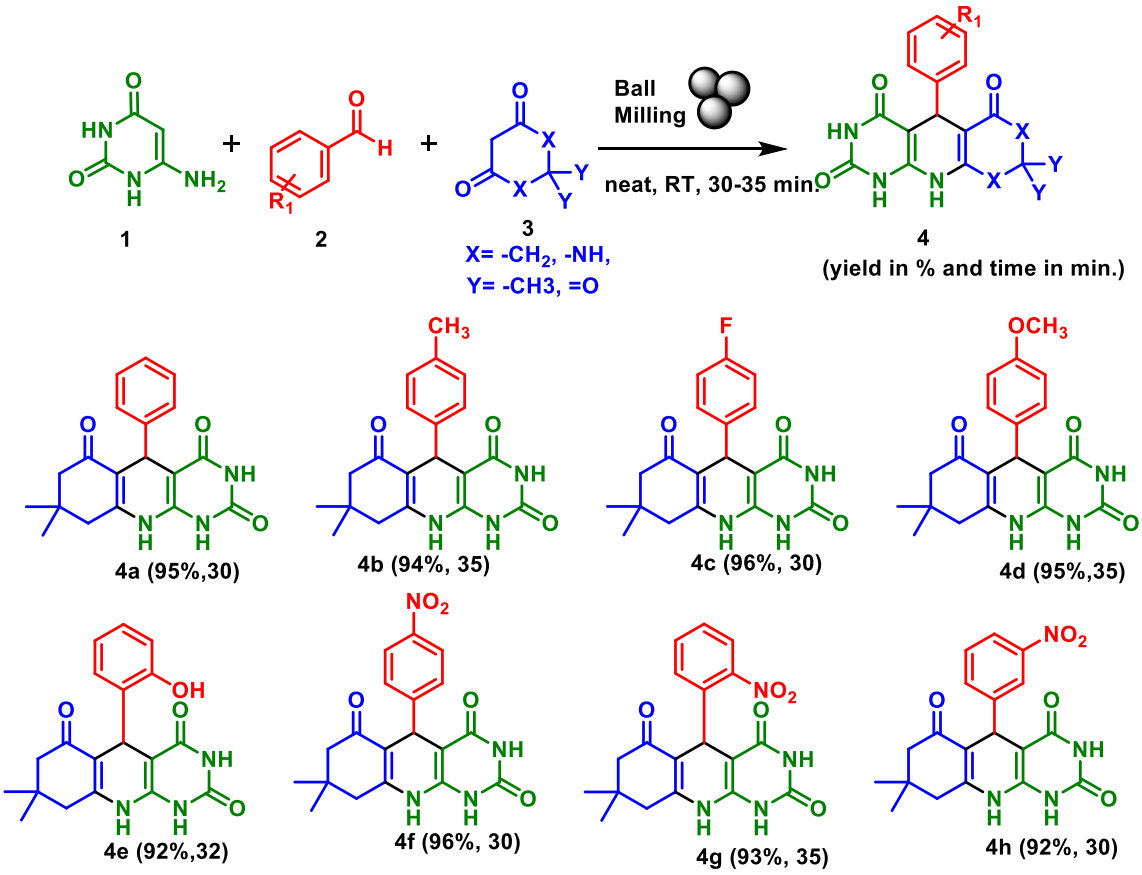
entry	catalyst (mol%)	solvent	condition	temperature (°C)	yield[b] (%)
11	Sulfamic acid (10 mol%)	EtOH	stirring	reflux	61
12	Sulfamic acid (10 mol%)	Neat	stirring	140	52
13	no catalyst	Neat	grinding[c]	RT	71
14	no catalyst	Neat	ball milling[d]	RT	82
15	no catalyst	Neat	ball milling[e]	RT	88
16	no catalyst	Neat	ball milling[f]	RT	92
17	no catalyst	Neat	ball milling[g]	RT	95
18	no catalyst	Neat	ball milling[h]	RT	88

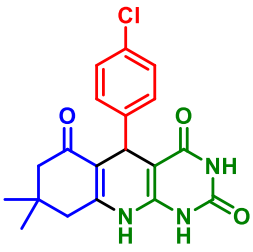
[a]Experimental condition: 6-aminouracil **1** (1 mmol), benzaldehyde **2a** (1 mmol) and dimedone **3a** (1 mmol) were subjected to ball milling for 30min. [b]Isolated yields. [c]grinding for 1h. [d]planetary ball-milling apparatus Retsch PM100 was employed using 10 balls (stainless steel, size 10 mm), 200 rpm, 2h. [e]ball milling at 400 rpm, 90min. [f]ball milling at 500 rpm, 60min. [g]ball milling at 650 rpm, 30min. [h]The reaction was carried out on the 10 mmol scale.

After the optimization of reaction conditions, the generality and range of the reaction were examined using a variety of benzaldehydes with different substituents, including -F, -Cl, -NO_2, -Me, and -OMe. The reaction always goes well and produces the desired products **4** and **5** with good to excellent yields (91–97%). This transition tolerated well the benzaldehyde derivatives with the electron-withdrawing (-NO_2, -F) and electron-donating (-OMe, -Me) groups on the benzene ring (Table 4.2 and 4.3). The position of the substituents on the

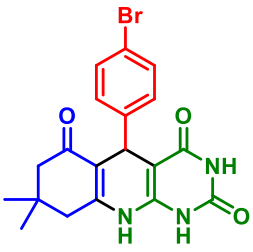
benzaldehyde's aromatic ring had a minimal impact on the reaction's efficiency. The substrate, which had nitro, fluoro, methoxy, chloro, and methyl substituents at the para position on the benzaldehyde backbone, readily reacted and, giving 95 to 97% yield, produced the corresponding products **4** and **5**.

Table 4.2 Substrate scope of Pyrimido [4,5-b]quinolines

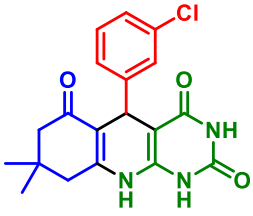




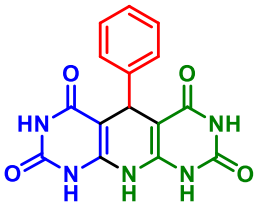
4i (92%, 30)



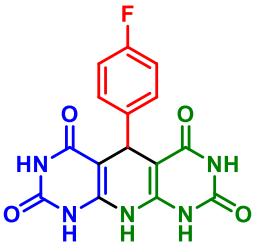
4j (92%, 35)



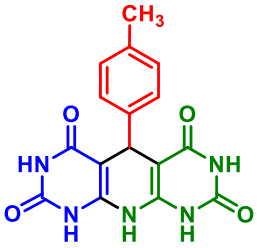
4k (93%, 32)



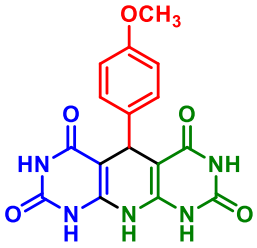
4l (94%, 30)



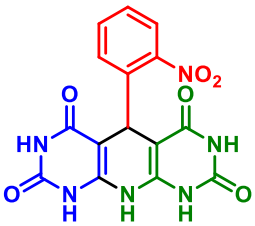
4m (95%, 30)



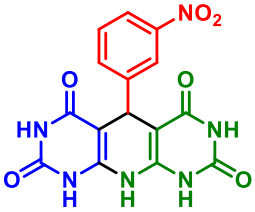
4n (94%, 30)



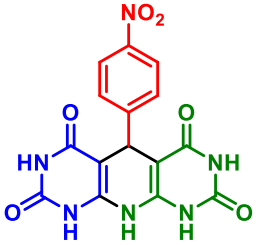
4o (95%, 30)



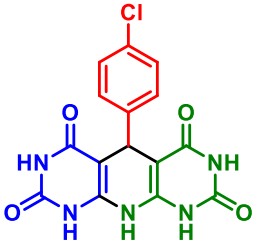
4p (92%, 35)



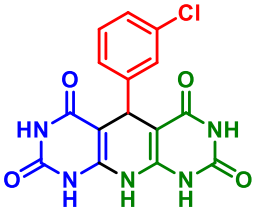
4q (93%, 32)



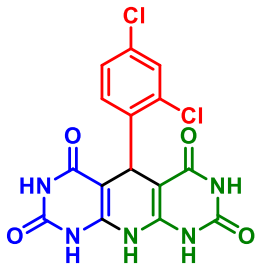
4r (97%, 30)



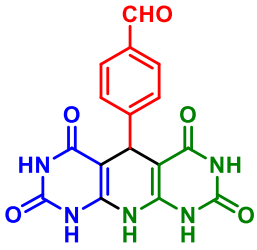
4s (95%, 32)



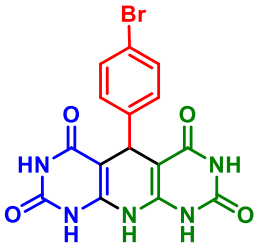
4t (93%, 35)



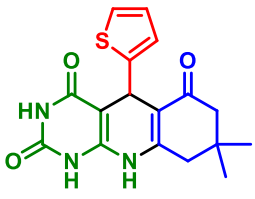
4u (95%, 30)



4v (92%, 32)



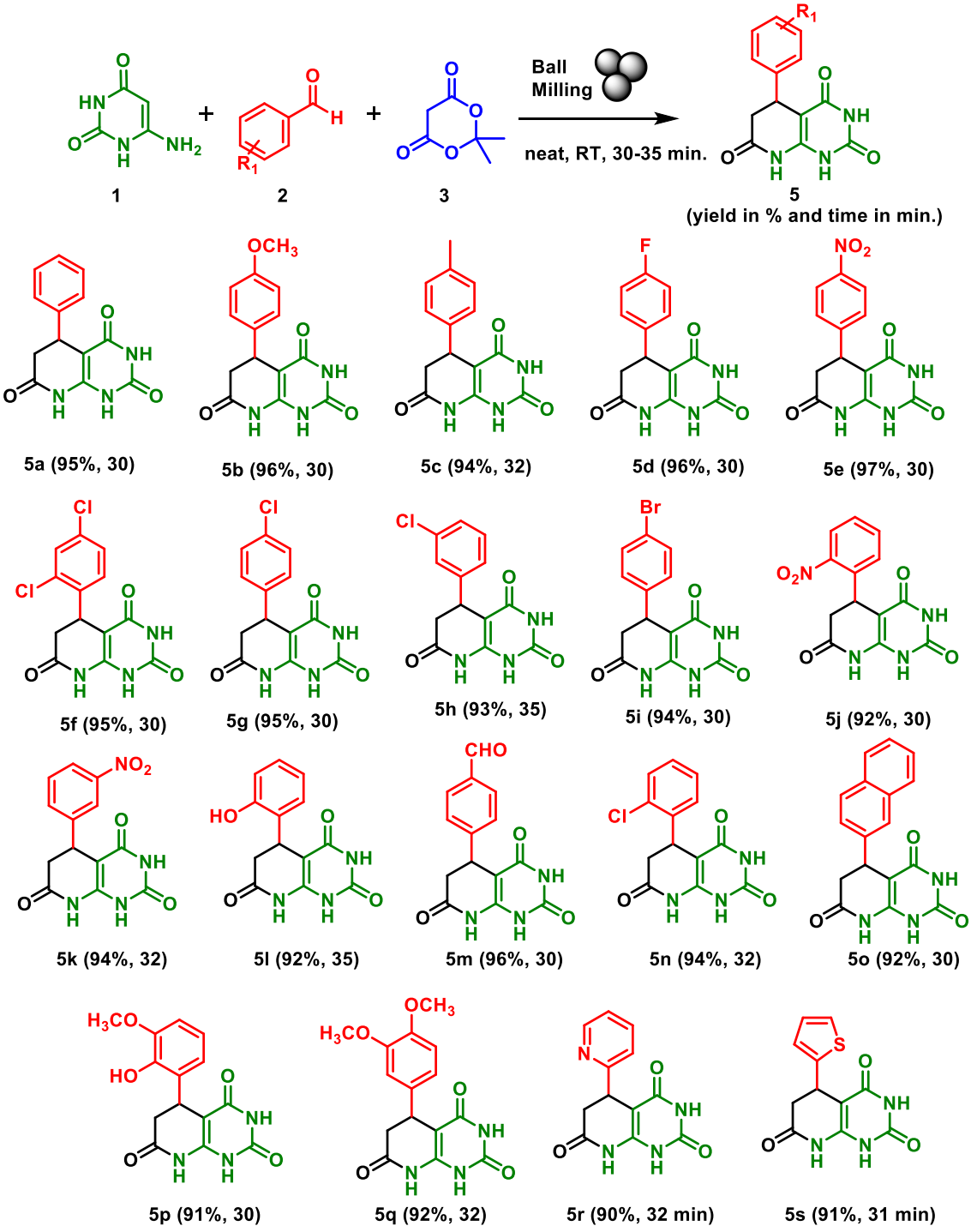
4w (94%, 30)



4x (89%, 30 min)

Reaction condition: 6-aminouracil **1** (1 mmol), benzaldehyde **2** (1 mmol) and dimedone **3a** (1 mmol) were subjected to ball milling at 650 rpm for 30-35 min.

Table 4.3 Substrate scope of Pyrido [2,3-d] pyrimidines



Reaction condition: 6-aminouracil **1** (1 mmol), benzaldehyde **2** (1 mmol) and Meldrum,s acid **3** (1 mmol) were subjected to ball milling at 650 rpm for 30-35 min.

Impact of milling speed (rpm) and the number of balls Milling speed (rpm), milling time, and the number of balls are the three factors in ball milling that are most crucial.[13] The reaction was milled using 10 mm balls at 650 rpm for 30 minutes to achieve the highest yield. The reaction yield was constant and decreased whenever one of these parameters changed.(Table 4.4)

Impact of Ball Mass and Material Three different ball materials have been used, mainly stainless steel, brass, and copper. The kinetics can be affected by the ball's material. To obtain more impact energy, balls of higher density have been used.[56,57]

Table 4.5 shows the properties of the balls used for the experiments in **Figure 4.1**. This figure illustrates that this response is unaffected by the ball's composition. On the other hand, altering the ball's mass causes a significant impact. When a heavier ball is used, the reaction happens more quickly. Results with a 107g stainless steel ball compared to 92 and 59g, respectively, clearly show considerable conversion and an increase in the reaction rate. This is consistent with the idea that using a heavier ball can speed up and improve grinding efficiency.[10,58] (Table 4.5)

Table 4.4 Effect of number of milling balls on the yield of the product **4a**

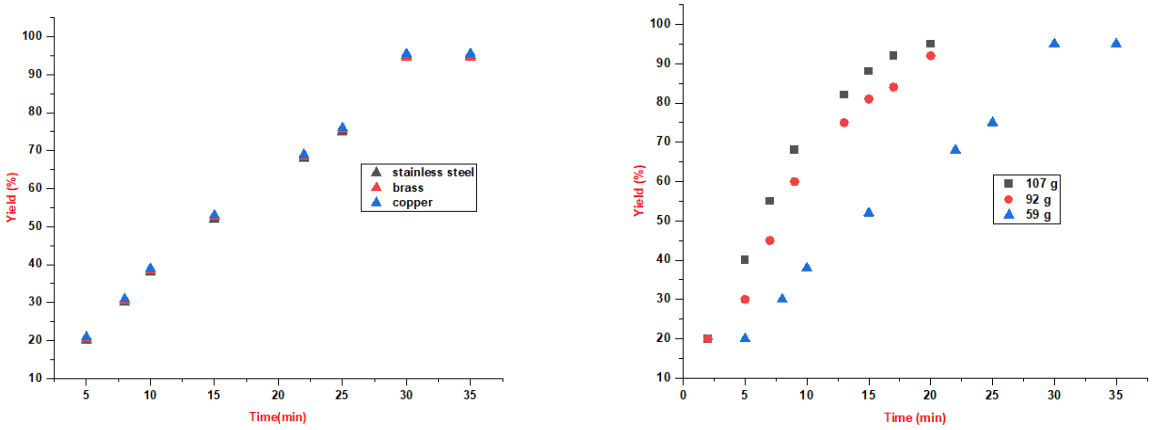
Entry	Number of milling balls	Yield (%)
1	2	0
2	4	trace
3	6	24
4	8	38
5	**10**	**95**
6	12	95
7	14	95

We are pleased to report that air or moisture did not affect the reactions, and the compounds could be purified without using a traditional column chromatographic method. After the reaction was completed, the unwanted crude products were removed and properly cleaned with an ethanol and hexane solution before being recrystallized to obtain the pure desired products. The spectral data of those compounds describes the characterization of new compounds and the comparison of known synthesized compounds to earlier spectral data.

Table 4.5 Effect of Milling Ball material and ball mass on the product **4a**

milling ball	ball material	ball mass (g)[a]
BR	brass	59
CU	copper	59
SS1	stainless steel	59
SS2	stainless steel	107
SS3	stainless steel	92

[a]All balls have the same diameter (10 mm) and are empty. They are filled with different solids (sand) to change their mass



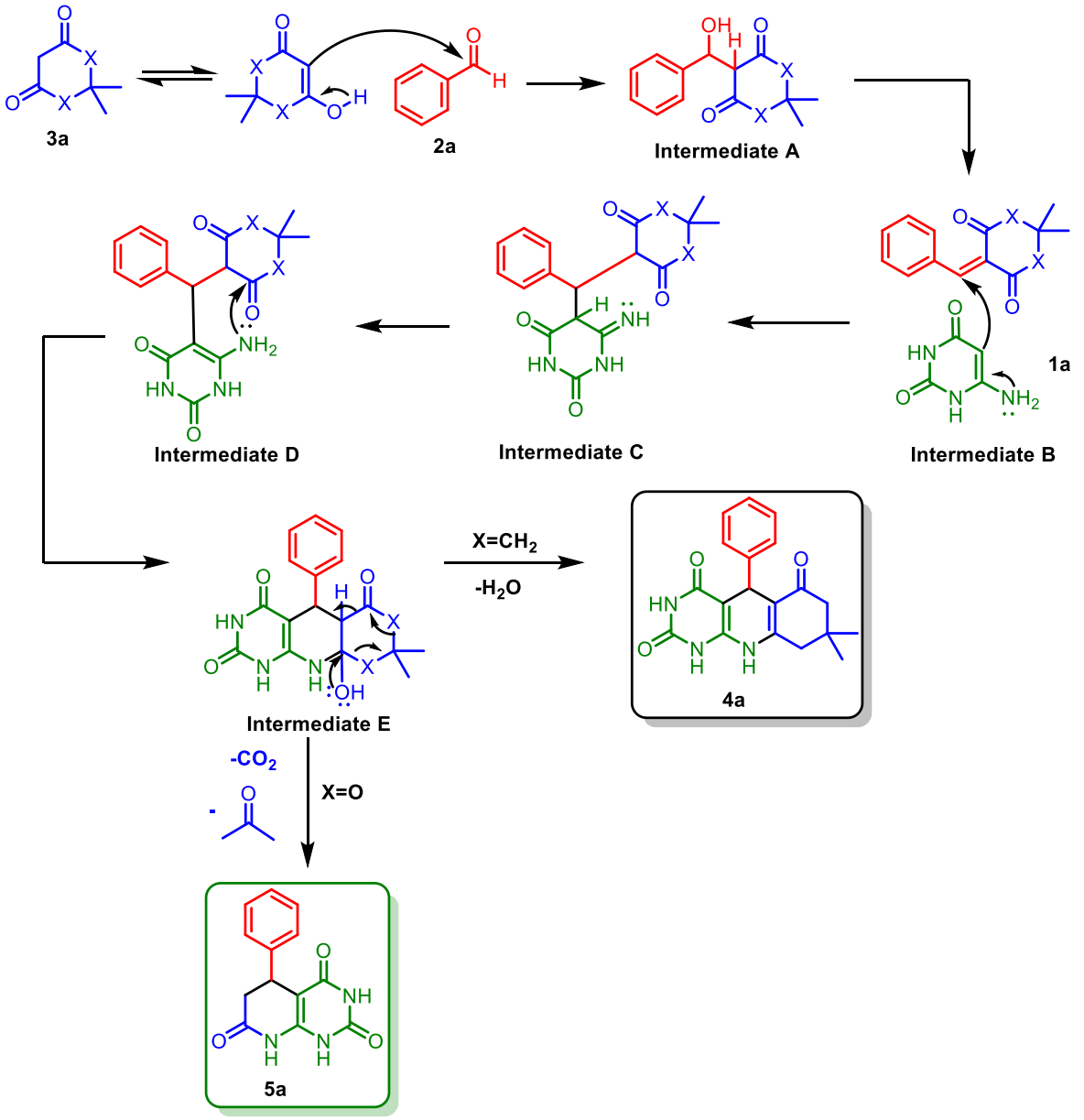
(a) **(b)**

Figure 4.1 Effect of the ball (a) material and (b) mass (Table 4.5) on the mechanochemical synthesis of pyrimido [4,5-b] quinolines and pyrimido [2,3-d] pyrimidines

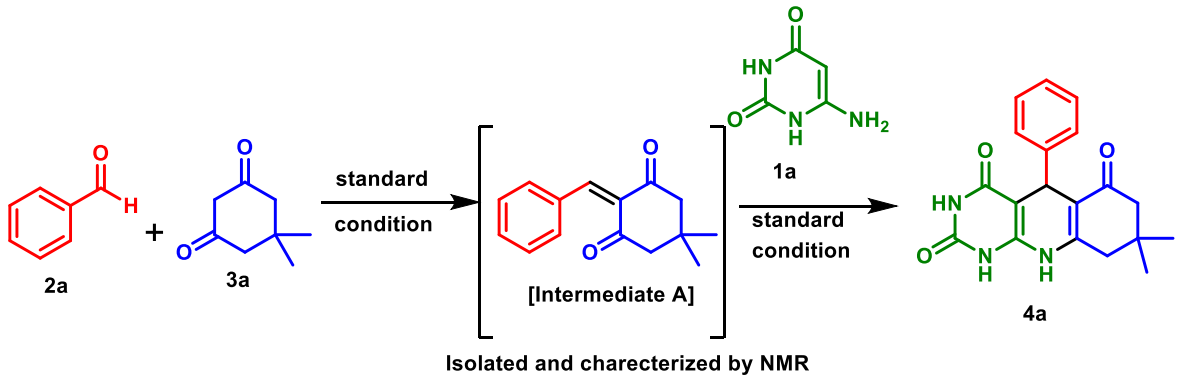
4.3 Proposed Mechanism

According to previous literature,[42,47] the plausible mechanism for the reaction is depicted in **Scheme 4.2**. Due to high milling energy, Knoevenagel condensation occurs between 1, 3-diketo compound and benzaldehyde to form an arylidene intermediate **(A)**. Now intermediate **A** undergoes Michael addition with 6-aminouracil to form intermediate **(C)**, which cyclized to form intermediate **(D).** This intermediate **D** gives either **4a** [(***I)*** if 1, 3 diketo compound is dimedone or barbituric acid after the elimination of H_2O molecules], or **5a [*(II)*** when 1, 3 diketo compound is Meldrum's acid after the release of acetone and CO_2 molecules.]

In order to confirm the formation of intermediate **A**, we carried out a stepwise reaction. As a first step, we isolated intermediate **A**, which was produced by the reaction of benzaldehyde and dimedone, and characterized it using NMR. We obtained good yields of the corresponding three-component product when the third component, 6-aminouracil, was added in **A** under our standard reaction conditions (**Scheme 4.3**).



Scheme 4.2 Plausible mechanism



Scheme 4.3 Stepwise reaction for the synthesis of **4a**

4.4 Conclusions

In conclusion, a valuable and practical multicomponent method has been devised for the production of biologically active N-heterocyclic Pyrimido [4,5-b] Quinolines and Pyrido [2,3-d] Pyrimidines using a ball mill from 6-aminouracil, aromatic aldehyde, and 1,3 diketones (dimedone, barbituric acid, and Meldrum's acid). It discusses an organic synthesis method that is somewhat more advanced (ball milling). High product yields in a short period during the reaction, a wide range of substrate scope, catalyst-free, solvent-free reaction, comfortable conditions, reduced energy consumption, a straightforward workup procedure, and purification by recrystallization instead of column chromatography are the green factors of this procedure. These characteristics render this approach a valuable substitution for the current ones.

4.5 Experimental Procedures

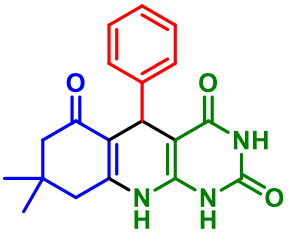
4.5.1 General procedure for the preparation of compounds 4a-4w & 5a-5q

A reaction chamber was set up using a 50 mL grinding beaker and milling balls (10×10 mm). A mixture of aromatic aldehydes, 6-amino uracil, and 1, 3-diketo compounds were milled

for 30-35 minutes at 650 rpm at room temperature for each reaction. The obtained solid product was filtered off through a Büchner funnel following the reaction's completion (monitored by thin-layer chromatography) and thoroughly washed with a solution of ethanol and hexane (1:4).

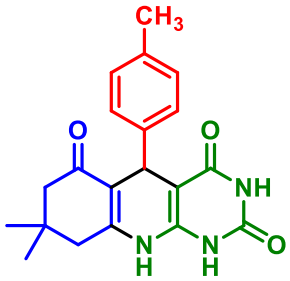
4.6 Characterization of products

8,8-dimethyl-5-phenyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4a)



White solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3401, 3251, 3191, 2931, 1651. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.73 (s, 1H), 10.22 (s, 1H), 8.79 (s, 1H), 7.19 (d, J = 4.3 Hz, 4H), 7.12 – 7.05 (m, 1H), 4.75 (s, 1H), 2.46 (d, J = 12.2 Hz, 2H), 2.21 (d, J = 16.1 Hz, 1H), 2.02 (d, J = 16.1 Hz, 1H), 1.03 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 194.71, 165.12, 163.12, 150.30, 149.88, 146.62, 128.19, 128.01, 126.37, 111.57, 89.70, 50.61, 33.47, 32.60, 29.42, 26.92. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{20}N_3O_3$ 338.1504; found: 338.1514.

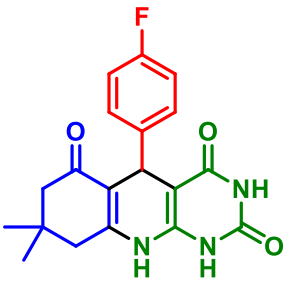
8,8-dimethyl-5-(p-tolyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinolone-2,4,6(1H,3H,7H)-trione (4b)



Off-white solid (94%), mp >300°C. IR (KBr, cm^{-1}): 3402, 3252, 3192, 2932, 1653. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.73 (s, 1H), 10.22 (s, 1H), 8.79 (s, 1H), 7.95 (d, 2H), 7.53 (d, 2H) 2.47 (d, J = 12.2 Hz, 2H), 2.22 (d, J = 16.1 Hz, 1H), 2.03 (d, J = 16.1 Hz, 1H),

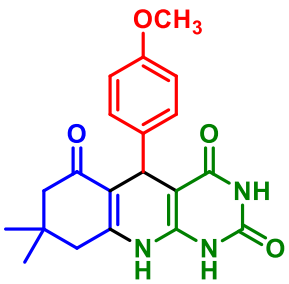
1.04 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 194.66, 170.82, 166.14, 163.12, 149.60, 133.67, 130.41, 129.52, 129.17, 115.33, 90.28, 61.15, 44.37, 32.56, 29.45, 26.92, 20.99, 14.67. HRMS (ESI) m/z: [M+H] + calculated for $C_{20}H_{23}N_3O_3$ 352.1661; found: 352.1664.

5-(4-fluorophenyl)-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4c)



Brown solid (96%), mp >300°C. IR (KBr, cm^{-1}): 3402, 3252, 3192, 2932, 1652. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.75 (s, 1H), 10.24 (s, 1H), 8.79 (s, 1H), 7.22 – 7.17 (m, 2H), 7.01 (t, J = 8.9 Hz, 2H), 4.74 (s, 1H), 2.48 – 2.39 (m, 2H), 2.09 (s, 2H), 1.06 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 194.81, 163.13, 161.92, 159.97, 150.24, 149.73, 144.22, 129.75, 129.68, 114.89, 114.72, 111.60, 89.93, 56.49, 50.47, 32.95, 32.59, 29.29, 26.93. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{19}FN_3O_3$ 356.1410; found: 356.1418.

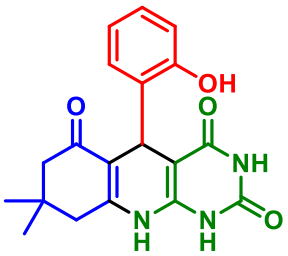
5-(4-methoxyphenyl)-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4d)



Yellow solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3403, 3253, 3193, 2933, 1653. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.71 (s, 1H), 10.18 (s, 1H), 8.71 (s, 1H), 7.09 (d, J = 8.6 Hz, 2H), 6.74 (d, J = 11.6 Hz, 2H), 4.69 (s, 1H), 3.34 (s, 3H), 2.44 (d, J = 14.3 Hz, 2H), 2.13 (dd, J = 68.4, 22.8 Hz, 2H), 1.02 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 194.79, 163.24, 157.86, 150.29, 149.30, 144.01, 139.25, 129.14, 113.56,

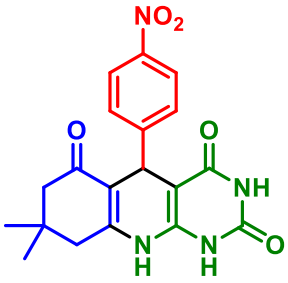
111.92, 90.36, 56.20, 55.37, 50.63, 32.59, 32.55, 29.53, 26.96. HRMS (ESI) m/z: [M+H] + calculated for $C_{20}H_{22}N_3O_4$ 368.1610; found: 368.1618.

5-(2-hydroxyphenyl)-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4e)



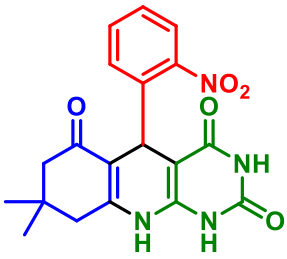
Light Brown solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3404, 3254, 3194, 2934, 1654. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.71 (s, 1H), 10.18 (s, 1H), 9.80 (s, 1H), 8.71 (s, 1H), 7.17 (t, *J* = 5.8 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.96 (d, *J* = 8.1 Hz, 1H), 4.67 (s, 1H), 2.43 (s, 2H), 2.12 (s, *J* = 91.2 Hz, 2H), 1.03 (s, 3H), 0.90 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 194.79, 164.38, 163.17, 157.86, 150.29, 149.34, 144.10, 139.15, 137.95, 128.92, 113.64, 112.01, 89.98, 56.04, 50.81, 35.98, 32.64, 29.35, 26.96. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{20}N_3O_4$ 354.1453; found: 354.1450.

8,8-dimethyl-5-(4-nitrophenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4f)



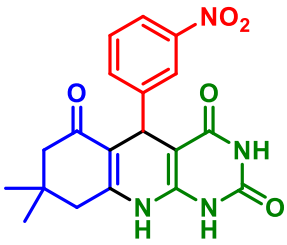
Off-white solid (96%), mp >300°C. IR (KBr, cm^{-1}): 3405, 3255, 3195, 2936, 1655. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.60 (s, 2H), 10.41 (s, 1H), 8.09 (d, *J* = 8.9 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 2H), 4.86 (s, 1H), 2.45 (d, 2H), 2.12 (d, 2H), 1.02 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 194.69, 165.04, 160.01, 154.86, 150.18, 149.32, 145.75, 128.41, 123.35, 110.50, 85.37, 50.54, 33.45, 32.67, 29.12, 27.10. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{19}N_4O_5$ 383.1355; found: 383.1348.

8,8-dimethyl-5-(2-nitrophenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4g)



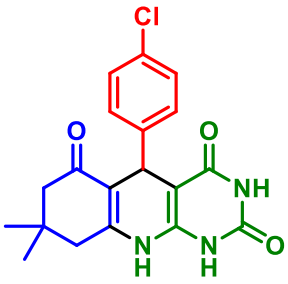
Reddish brown solid (93%), mp >300°C. IR (KBr, cm^{-1}): 3406, 3256, 3196, 2936, 1656. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.68 (s, 1H), 10.38 (s, 1H), 8.88 (s, 1H), 7.74 (d, J = 7.3 Hz, 1H), 7.60 – 7.50 (m, 2H), 7.34 – 7.30 (m, 1H), 4.96 (s, 1H), 2.16 (s, 2H), 1.98 (s, 2H), 1.02 (s, 3H), 0.88 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 194.70, 163.80, 162.96, 150.04, 148.91, 141.81, 133.04, 131.06, 127.21, 124.07, 111.00, 89.41, 50.82, 32.56, 32.23, 29.09, 27.11, 19.05. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{19}N_4O_5$ 383.1355; found: 383.1360.

8,8-dimethyl-5-(3-nitrophenyl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4h)



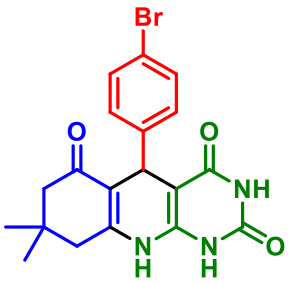
Light orange solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3408, 3257, 3198, 2939, 1658. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.75 (s, 1H), 10.24 (s, 1H), 8.79 (s, 1H), 8.01 (d, J = 7.3 Hz, 1H), 7.85 (s, 1H), 7.57 – 7.54 (m, 2H), 4.49 (s, 1H), 2.46 (s, 2H), 2.09 (s, 2H), 1.06 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 196.34, 165.81, 160.13, 154.77, 150.26, 148.29, 142.81, 134.28, 129.62, 121.62, 120.76, 110.50, 85.63, 56.48, 45.44, 32.76, 28.43, 24.33, 21.65. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{19}N_4O_5$ 383.1355; found: 383.1350.

5-(4-chlorophenyl)-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4i)



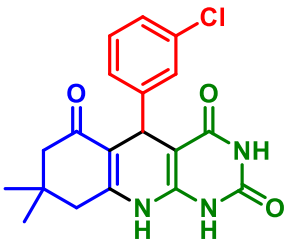
White solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3409, 3259, 3199, 2939, 1659. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.30 (s, 1H), 10.14 (s, 1H), 8.79 (s, 1H), 7.20 (s, 1H), 7.10 (d, 2H), 6.90 (s, 1H), 4.32 (s, 1H), 2.13 (s, 2H), 1.93 (s, 1H), 1.80 (s, 1H), 1.03 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 195.38, 169.09, 167.91, 163.33, 159.68, 143.63, 138.66, 132.04, 124.85, 112.98, 76.18, 56.50, 32.19, 32.10, 27.58, 13.70. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{19}ClN_3O_3$ 372.1114; found: 372.1118.

5-(4-bromophenyl)-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4j)



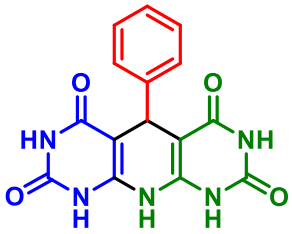
White solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3400, 3250, 3190, 2930, 1650. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.75 (s, 1H), 10.24 (s, 1H), 8.79 (s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.2 Hz, 2H), 4.74 (s, 1H), 2.45 (d, 2H), 2.09 (d, 2H), 1.03 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 194.01, 169.09, 167.98, 162.95, 159.78, 143.55, 132.36, 127.15, 122.54, 110.20, 78.72, 59.06, 51.12, 32.19, 31.73, 18.96, 13.71. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{19}BrN_3O_3$ 416.0609; found: 416.0613.

5-(3-chlorophenyl)-8,8-dimethyl-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4k)



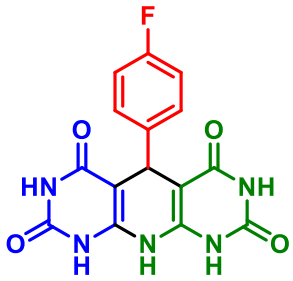
White solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3409, 3259, 3199, 2939, 1659. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.30 (s, 1H), 10.14 (s, 1H), 8.79 (s, 1H), 7.25 (t, J = 8.6 Hz, 1H), 7.16 (s, 1H), 7.05 (m, 2H), 4.32 (s, 1H), 2.13 (s, 2H), 1.93 (s, 1H), 1.80 (s, 1H), 1.03 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 195.38, 169.09, 167.91, 163.33, 159.68, 143.63, 138.66, 132.04, 124.85, 112.98, 76.18, 56.50, 32.19, 32.10, 27.58, 13.70. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{19}ClN_3O_3$ 372.1114; found: 372.1116.

5-phenyl-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4l)



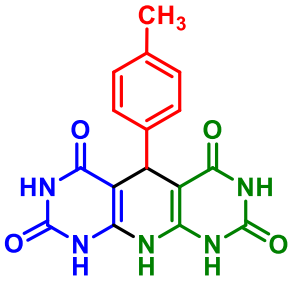
Reddish brown solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3410, 3210, 3110, 2910, 1610. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.508 (s, 2H), 10.308 (s, 2H), 7.22 (m, J = 9.0 Hz, 2H), 7.07 (m, J = 9.0 Hz, 3H), 6.64 (s, 1H), 5.31 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 154.72, 150.32, 145.28, 139.81, 128.10, 126.99, 125.36, 89.69, 32.97. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{12}N_5O_4$ 326.0889; found: 326.0888.

5-(4-fluorophenyl)-5,10-dihydropyrido[2, 3-d:6, 5-d']dipyrimidine-2,4,6,8 (1H, 3H, 7H, 9H)-tetraone (4m)



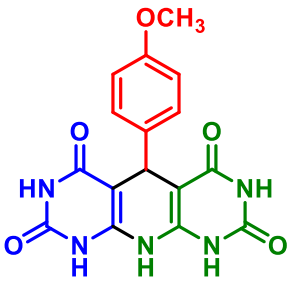
Light orange solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3420, 3220, 3120, 2920, 1620. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.53 (s, 2H), 10.32 (s, 2H), 7.07 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 6.66 (s, 1H), 5.27 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 161.76, 159.09, 150.20, 141.41, 128.83, 128.80, 114.55, 86.14, 32.20. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{11}FN_5O_4$ 344.0795; found: 326.0889.

5-(p-tolyl)-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4n)



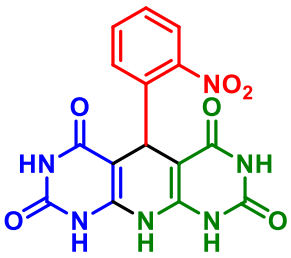
76% yield. Pale yellow solid. m.p.: 177-180 °C. IR (KBr, cm^{-1}): 3431, 3218, 3121, 2932, 1620. ^{1}H NMR (500 MHz, DMSO-d^6) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 2H), 7.17 (s, 1H), 7.13 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.0, 0.8 Hz, 1H), 7.00 (dd, *J* = 8.1, 1.2 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 144.31, 137.85, 135.74, 134.92, 130.34, 129.85, 127.27, 125.24, 120.98, 118.97, 21.59. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{13}N_2O_4S$ 293.0596; found: 293.0597.

5-(4-methoxyphenyl)-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4o)



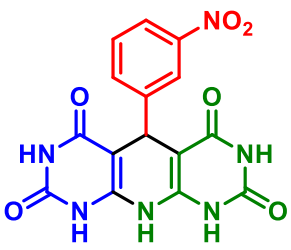
Orange solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3431, 3231, 3131, 2931, 1631. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.48 (s, 2H), 10.28 (s, 2H), 8.26 (s, 1H), 7.07 (d, J = 9.0 Hz, 2H), 6.77 (d, J = 8.8 Hz, 2H), 5.25 (s, 1H), 3.87 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.39, 162.66, 155.04, 150.72, 138.27, 125.64, 114.43, 79.41, 56.17, 31.90. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{14}N_5O_5$ 356.0994; found: 356.0999.

5-(2-nitrophenyl)-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4p)



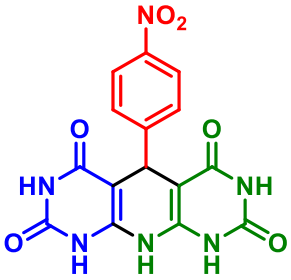
Yellow solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3411, 3221, 3131, 2941, 1650. ^{1}H NMR (500 MHz, DMSO-d^6) δ 11.52 (s, 2H), 11.30 (s, 2H), 9.02 (s, 1H), 8.15 (d, J = 14.7 Hz, 1H), 7.45 – 7.34 (m, 2H), 7.14 (ddd, J = 8.2, 6.9, 1.1 Hz, 1H), 4.17 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 162.72, 162.21, 151.12, 150.71, 139.51, 133.57, 130.32, 127.16, 125.66, 79.99, 31.13. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{11}N_6O_6$ 371.0740; found: 371.0743.

5-(3-nitrophenyl)-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4q)



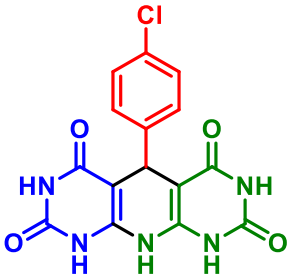
Brown solid (93%), mp >300°C. IR (KBr, cm^{-1}): 3410, 3220, 3130, 2940, 1650. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.63 (s, 2H), 10.44 (s, 2H), 8.01 (d, J = 7.8 Hz, 1H), 7.85 (s, 1H), 7.58 – 7.52 (m, 2H), 6.76 (s, 1H), 5.40 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 162.84, 161.79, 150.17, 147.96, 143.16, 133.66, 129.64, 121.56, 120.71, 79.99, 30.86. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{11}N_6O_6$ 371.0740; found: 371.0746.

5-(4-nitrophenyl)-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4r)



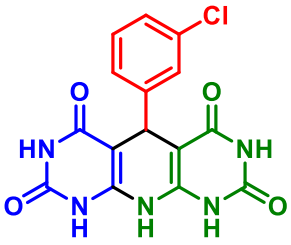
White solid (97%), mp >300°C. IR (KBr, cm^{-1}): 3450, 3240, 3130, 2920, 1610. ^{1}H NMR (500 MHz, DMSO-d^6) δ 11.18 (s, 2H), 10.91 (s, 2H), 8.12 (d, J = 8.9 Hz, 2H), 7.45 (d, J = 8.0 Hz, 8H), 6.73 (s, 1H), 5.37 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 169.068, 167.167, 150.110, 149.382, 145.836, 128.567, 123.683, 80.477, 31.412. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{11}N_6O_6$ 371.0740; found: 371.0738.

5-(4-chlorophenyl)-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4s)



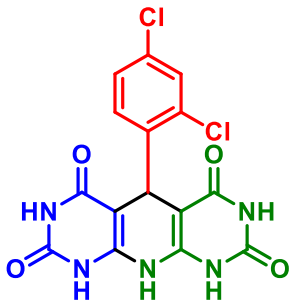
White solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3400, 3201, 3102, 2903, 1604. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.54 (s, 2H), 10.34 (s, 2H), 7.25 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 6.67 (s, 1H), 5.28 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 163.11, 161.21, 150.21, 139.13, 129.93, 129.02, 127.99, 86.15, 32.19. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{11}ClN_5O_4$ 360.0499; found: 360.0503.

5-(3-chlorophenyl)-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4t)



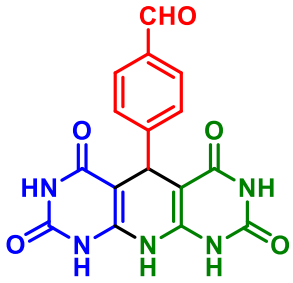
White solid (93%), mp >300°C. IR (KBr, cm^{-1}): 3409, 3210, 3111, 2912, 1613. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.56 (s, 2H), 10.36 (s, 2H), 7.25 (t, J = 8.1 Hz, 1H), 7.17 (d, J = 9.7 Hz, 1H), 7.09 – 7.01 (m, 2H), 6.69 (s, 1H), 5.29 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 151.525, 148.795, 135.187, 133.186, 130.171, 127.232, 126.400, 125.298, 91.384, 31.414. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{11}ClN_5O_4$ 360.0499; found: 360.0501.

5-(2,4-dichlorophenyl)-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4u)



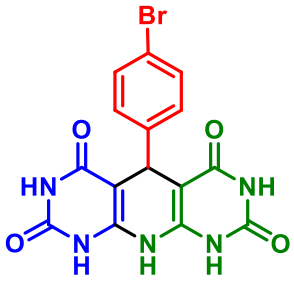
Off-white solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3415, 3216, 3117, 2918, 1619. ^{1}H NMR (500 MHz, DMSO-d^6) δ 11.05 (s, 2H), 10.90 (s, 2H), 7.49 (s, 1H), 7.39 – 7.30 (m, 2H), 6.56 (s, 1H), 5.25 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 155.55, 153.71, 142.59, 136.91, 133.67, 131.54, 129.02, 126.37, 81.05, 30.84. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{10}Cl_2N_5O_4$ 394.0109; found: 394.0114.

4-(2,4,6,8-tetraoxo-1,2,3,4,5,6,7,8,9,10-decahydropyrido[2,3-d:6,5-d']dipyrimidin-5-yl)benzaldehyde (4v)



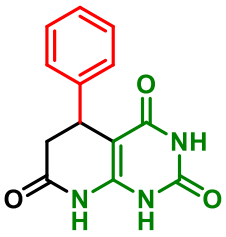
Brown solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3420, 3221, 3122, 2923, 1624. ^{1}H NMR (500 MHz, DMSO-d^6) δ 11.05 (s, 2H), 10.87 (s, 1H), 10.80 (s, 1H), 9.98 (s, 1H), 8.98 (s, 1H), 6.96 (d, J = 24.6 Hz, 2H), 6.66 (d, J = 34.4 Hz, 2H), 5.22 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 192.30, 166.10, 160.94, 155.82, 150.74, 133.16, 129.35, 126.64, 82.39, 30.85. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{12}N_5O_5$ 354.0838; found: 354.0833.

5-(4-bromophenyl)-5,10-dihydropyrido[2,3-d:6,5-d']dipyrimidine-2,4,6,8(1H,3H,7H,9H)-tetraone (4w)



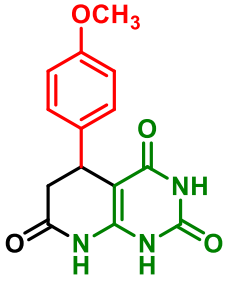
White solid (94%), mp >300°C. IR (KBr, cm^{-1}): 3437, 3238, 3139, 2940, 1641.^{1}H NMR (500 MHz, DMSO-d^6) δ 10.54 (s, 2H), 10.34 (s, 2H), 7.42 (s, 1H), 7.38 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 5.26 (s, 1H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 150.28, 139.83, 132.90, 131.65, 130.89, 129.48, 118.14, 90.94, 32.69. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{11}BrN_5O_4$ 402.9916; found: 402.9911.

5-phenyl-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5a)



White solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3260, 3160, 1710, 1480, 750. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.49 (s, 2H), 10.29 (s, 1H), 7.39 (t, J = 4.3 Hz, 1H), 7.02 – 6.94 (m, 4H), 4.14 (s, 1H), 2.24 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 169.84, 159.85, 150.20, 146.14, 136.71, 134.02, 130.21, 126.93, 86.44, 36.51, 32.48. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{12}N_3O_3$ 258.0878; found: 258.0872.

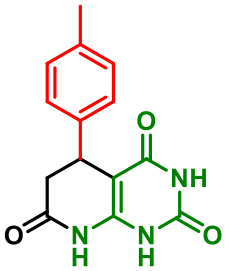
5-(4-methoxyphenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5b)



White solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3264, 3164, 1714, 1484, 754. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.48 (s, 1H), 10.28 (s, 1H), 9.88 (s, 1H), 7.07 (d, J = 13.7 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 8.7 Hz, 2H), 4.50 (s, 1H), 3.68 (s, 3H), 2.07 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 169.35, 166.09, 160.15, 149.88, 145.27, 135.29, 127.79,

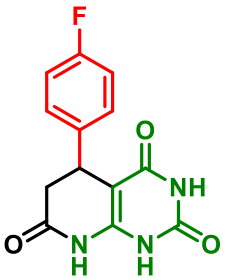
113.42, 85.08, 55.13, 35.94, 31.91. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_{14}N_3O_4$ 288.0984; found: 288.0989.

5-(p-tolyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5c)



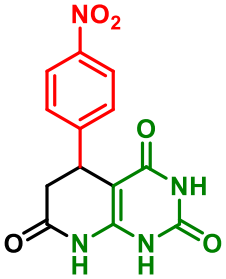
Brown solid (94%), mp >300°C. IR (KBr, cm^{-1}): 3265, 3165, 1715, 1485, 755 ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.49 (s, 2H), 10.29 (s, 1H), 7.01 (d, J = 8.1 Hz, 2H), 6.95 (d, J = 7.8 Hz, 2H), 4.12 (s, 1H), 2.41 (s, 2H, CH_2), 2.24 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 169.84, 164.18, 150.24, 145.56, 136.77, 133.99, 130.21, 130.07, 86.16, 36.51, 32.50, 20.93. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_{14}N_3O_3$ 272.1035; found: 272.1035.

5-(4-fluorophenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5d)



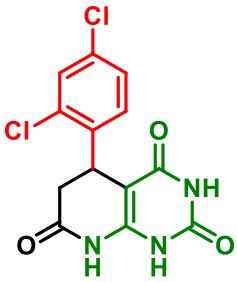
White solid (96%), mp >300°C. IR (KBr, cm^{-1}): 3266, 3166, 1716, 1486, 757**.** ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.60 (s, 2H), 10.40 (s, 1H), 8.09 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 8.8 Hz, 2H), 4.53 (s, 1H), 2.11 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 165.85, 161.62, 159.65, 150.25, 135.87, 128.80, 114.74, 114.58, 86.71, 36.79, 32.76. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{11}N_3O_3F$ 276.0784; found: 276.0788.

5-(4-nitrophenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5e)



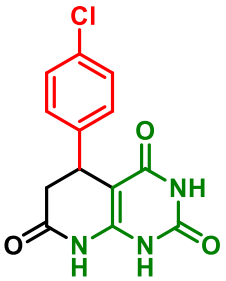
White solid (97%), mp >300°C. IR (KBr, cm^{-1}): 3268, 3168, 1718, 1488, 758. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.51 (s, 2H), 10.31 (s, 1H), 7.09 (d, J = 8.7 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 4.64 (s, 1H), 2.09 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 166.66, 161.21, 150.17, 149.33, 147.47, 145.75, 128.42, 123.35, 85.93, 37.09, 33.56. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{11}N_4O_5$ 303.0729; found: 303.0725.

5-(2,4-dichlorophenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5f)



White solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3269, 3169, 1719, 1487. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.42 (s, 3H), 7.42 (s, 1H), 7.30 (dd, J = 21.0, 7.8 Hz, 2H), 4.14 (s, 1H) 1.97 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 167.45, 154.40, 150.22, 138.36, 133.66 131.57, 131.07, 130.89, 129.13, 128.78, 126.94, 89.41, 36.96, 32.12. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{10}N_3O_3Cl_2$ 326.0099; found: 326.0094.

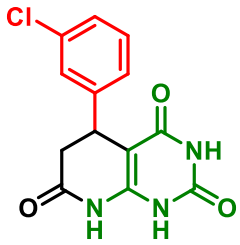
5-(4-chlorophenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5g)



White solid (95%), mp >300°C. IR (KBr, cm^{-1}): 3253, 3151, 1741, 1451, 751. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.55 (s, 2H), 10.35 (s, 1H), 7.25 (d, J = 8.6 Hz, 2H), 7.08 (d, J = 7.8 Hz, 2H), 4.05 (s, 1H), 2.05 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 166.94, 150.20, 139.16, 131.62,

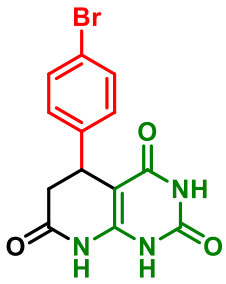
129.92, 129.23, 129.01, 127.99, 89.24, 37.07, 32.58. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{11}N_3O_3Cl$ 292.0488; found: 292.0484.

5-(3-chlorophenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5h)



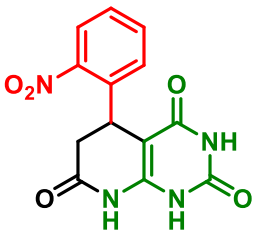
White solid (93%), mp >300°C. IR (KBr, cm^{-1}): 3276, 3178, 1713, 1485, 755. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.58 (s, 2H), 10.38 (s, 1H), 7.25 (t, J = 8.6 Hz, 1H), 7.16 (s, 1H), 7.05 (m, 2H), 4.37 (s, 1H), 2.21 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 165.82, 154.76, 150.27, 142.97, 133.05, 129.95, 128.29, 126.81, 125.87, 125.47, 86.16, 37.07, 32.76. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{11}N_3O_3Cl$ 292.0488; found: 292.0492.

5-(4-bromophenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5i)



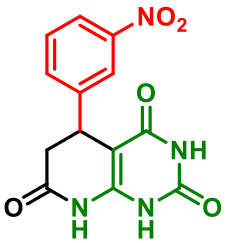
Off -white solid (94%), mp >300°C. IR (KBr, cm^{-1}): 3275, 3170, 1720, 1489, 752. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.56 (s, 2H), 10.35 (s, 1H), 7.85 (d, J = 2.9 Hz, 2H, CH_2), 7.38 (d, J = 8.6 Hz, 2H), 3.89 (s, 1H), 2.21 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 171.15, 150.19, 139.62, 135.59, 132.80, 131.73, 130.89, 118.37, 89.69, 35.94, 32.76. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{11}N_3O_3Br$ 335.9983; found: 335.9988.

5-(2-nitrophenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5j)



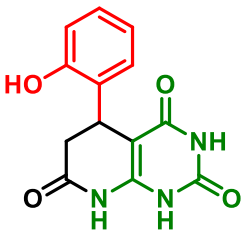
Brown solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3166, 3169, 1715, 1491, 761.^{1}H NMR (500 MHz, DMSO-d^6) δ 10.41 (s, 3H), 7.58 (d, J = 7.9 Hz, 1H), 7.54 (t, J = 7.2 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.9 Hz, 1H), 4.00 (s, 1H) 2.13 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 171.47, 162.35, 149.87, 134.69, 134.22, 131.96, 130.31, 127.07, 124.79, 123.99, 89.41, 37.08, 29.79. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{11}N_4O_5$ 303.0729; found: 303.0734.

5-(3-nitrophenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5k)



Yellow solid (94%), mp >300°C. IR (KBr, cm^{-1}): 3286, 3169, 1721, 1489, 759. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.64 (s, 1H), 10.46 (s, 2H), 8.01 (d, J = 6.9 Hz, 1H), 7.85 (s, 1H), 7.54 (dt, J = 15.7, 7.9 Hz, 2H), 3.98 (s, 1H), 2.1 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 170.91, 162.35, 150.15, 148.18, 146.12, 142.87, 134.29, 129.64, 121.69, 120.78, 85.37, 33.02, 31.20. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{11}N_4O_5$ 303.0729; found: 303.0728.

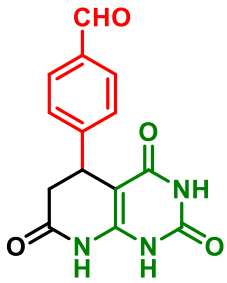
5-(2-hydroxyphenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5l)



Light Brown solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3388, 3182, 1722, 1376. ^{1}H NMR (500 MHz, DMSO-d^6) δ 11.68 (s, 1H), 10.87 (s, 1H), 9.96 (s, 2H), 7.17 (t, J = 5.8 Hz, 1H), 7.10 – 7.04 (m, 2H), 6.96 (d, J = 8.1 Hz, 1H), 6.45 (s, 2H), 4.01 (s, 1H), 2.21 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 163.93, 163.03, 155.11, 150.65, 150.12, 129.18, 127.79,

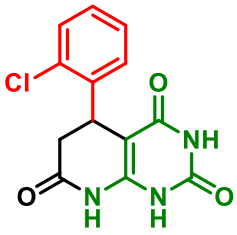
125.24, 125.03, 115.58, 90.25, 37.18, 27.15. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{12}N_3O_4$ 274.0827; found: 274.0831.

4-(2,4,7-trioxo-1,2,3,4,5,6,7,8-octahydropyrido[2,3-d]pyrimidin-5-yl)benzaldehyde (5m)



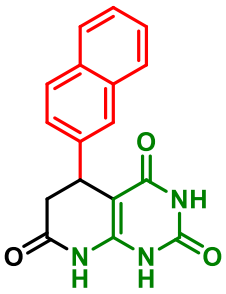
Off -white solid (96%), mp >300°C. IR (KBr, cm^{-1}): 3374, 3166, 1749, 785, 677**.** ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.59 (s, 2H), 10.40 (s, 1H), 9.94 (s, 1H), 7.77 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 7.8 Hz, 2H), 3.87 (s, 1H, diastereotopic CH), 2.09 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO) δ 193.06, 169.58, 150.24, 148.11, 140.25, 134.23, 130.46, 129.63, 127.83, 86.12, 37.57, 33.55. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_{12}N_3O_4$ 286.0827; found: 286.0823.

5-(2-chlorophenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5n)



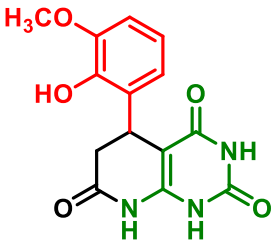
Reddish brown solid (94d%), mp >300°C. IR (KBr, cm^{-1}): 3315, 3159, 1721**.** ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.39 (s, 3H), 7.58 (d, *J* = 7.9 Hz, 1H), 7.54 (t, *J* = 7.2 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 3.90 (s, 1H), 2.05 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 167.66, 154.31, 150.10, 148.25, 138.99, 136.31, 132.88, 131.24, 129.77, 126.87, 86.14, 37.09, 31.89. HRMS (ESI) m/z: [M+H] + calculated for $C_{13}H_{11}N_3O_3Cl$ 292.0488; found: 292.0491.

5-(naphthalen-2-yl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5o)



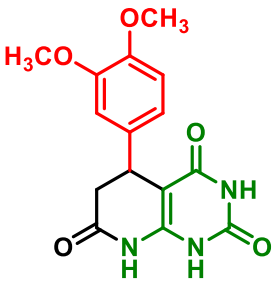
Light orange solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3380, 3170, 1712. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.56 (s, 1H), 10.38 (s, 2H), 7.82 (d, J = 9.3 Hz, 2H), 7.73 (d, J = 8.6 Hz, 1H), 7.54 (s, 1H), 7.41 (dd, J = 10.2, 6.5 Hz, 2H), 7.28 (d, J = 10.2 Hz, 1H), 4.00 (s, 1H), 2.21 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 168.89, 161.06, 150.29, 147.66, 137.90, 136.38, 135.06, 133.57, 130.10, 129.47, 128.48, 125.34, 124.31, 127.78, 86.73, 37.07, 32.76. HRMS (ESI) m/z: [M+H] + calculated for $C_{17}H_{14}N_3O_3$ 308.1035; found: 308.1039.

5-(2-hydroxy-3-methoxyphenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5p)



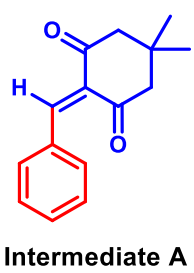
White solid (91%), mp >300°C. IR (KBr, cm^{-1}): 3350, 3150, 1637. ^{1}H NMR (500 MHz, DMSO-d^6) δ 11.69 (s, 1H), 10.83 (s, 1H), 9.93 (s, 1H), 6.99 (t, J = 7.9 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 6.64 (d, J = 7.5 Hz, 1H), 6.42 (s, 1H), 4.76 (s, 1H), 3.78 (s, 3H), 2.07 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 169.85, 164.19, 149.61, 146.91, 142.71, 139.52, 128.03, 120.34, 110.66, 86.73, 56.49, 35.17, 28.93. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_{14}N_3O_5$ 304.0933; found: 304.0930.

5-(3,4-dimethoxyphenyl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5q)



White solid (92%), mp >300°C. IR (KBr, cm^{-1}): 3321, 3155, 1705. ^{1}H NMR (500 MHz, DMSO-d^6) δ 11.32 (s, 1H), 11.20 (s, 1H), 8.42 (d, *J* = 1.8 Hz, 1H), 8.26 (s, 1H), 7.91 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 1H), 4.23(s, 1H), 3.89 (s, 3H), 3.81 (s, 3H), 2.40 (s, 2H, CH_2). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.47, 162.85, 155.91, 154.10, 150.67, 148.26, 132.17, 125.75, 117.25, 115.75, 111.56, 56.33, 55.88, 37.59, 29.56. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{16}N_3O_5$ 318.1089; found: 318.1086.

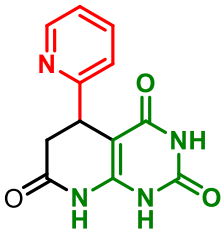
2-benzylidene-5,5-dimethylcyclohexane-1,3-dione (Intermediate A):



Intermediate A

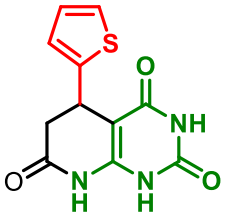
White solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (s, 1H), 7.30 (t, 2H), 7.23 (t, 2H), 7.11 (t, 1H), 2.48 (m, 2H), 2.29-2.15 (m, 2H), 1.12 (s, 3H), 1.01 (s, 3H), ^{13}C NMR (126 MHz, $CDCl_3$) δ 27.33, 29.26, 32.19, 40.87, 50.74, 123.66, 126.35, 128.03, 128.37, 139.25, 144.08, 190.37,192.08.

5-(pyridin-2-yl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5r):



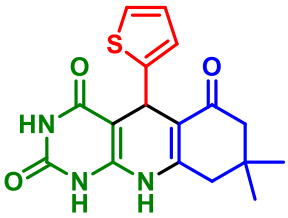
Yellow solid (90%), mp >300°C. IR (KBr, cm^{-1}): 3310, 3145, 1701. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.42 (s, 1H), 10.0 (s, 1H), 8.81 (s, 1H), 8.30 (d, *J* = 23.9 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 8.1 Hz, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 4.02 (s, 1H), 2.07 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 163.34, 161.52, 152.64, 150.78, 150.16, 140.70, 137.18, 131.10, 125.84, 92.10, 36.52, 31.41.

5-(thiophen-2-yl)-5,8-dihydropyrido[2,3-d]pyrimidine-2,4,7(1H,3H,6H)-trione (5s):



Ash grey solid (91%), mp >300°C. IR (KBr, cm^{-1}): 3311, 3146, 1711. ^{1}H NMR (500 MHz, DMSO- d^{6}) δ 10.53 (s, 2H), 10.31 (s, 1H), 7.22 (d, *J* = 5.1 Hz, 1H), 6.85 – 6.82 (m, 1H), 6.61 (d, *J* = 3.3 Hz, 1H), 4.05 (s, 1H), 2.66 (s, 2H). ^{13}C NMR (126 MHz, DMSO) δ 165.55, 154.41, 150.14, 146.08, 126.58, 123.82, 123.62, 87.33, 35.45, 30.45.

8,8-dimethyl-5-(thiophen-2-yl)-5,8,9,10-tetrahydropyrimido[4,5-b]quinoline-2,4,6(1H,3H,7H)-trione (4x):



Dark green solid (89%), mp >300°C. IR (KBr, cm^{-1}): 3436, 3239, 3133, 2949, 1643. ^{1}H NMR (500 MHz, DMSO- d^{6}) δ 10.82 (s, 1H), 10.30 (s, 1H), 8.95 (s, 1H), 7.24 (d, *J* = 5.0 Hz, 1H), 7.18 (d, *J* = 4.9 Hz, 1H), 6.74 (d, *J* = 3.2 Hz, 1H), 5.08 (s, 1H), 2.48 (d, *J* = 17.7 Hz, 1H), 2.36 (d, *J* = 17.5 Hz, 1H), 2.20 (d, *J* = 16.1 Hz, 1H), 1.97 (d, *J* = 16.0 Hz, 1H), 1.02 (s, 3H), 0.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 194.70, 163.91, 163.16, 150.93, 149.96, 148.52, 127.03, 123.96, 123.61, 111.43, 89.64, 50.55, 32.55, 32.28, 29.52, 29.22, 26.92.

4.7 Spectral Data of few products

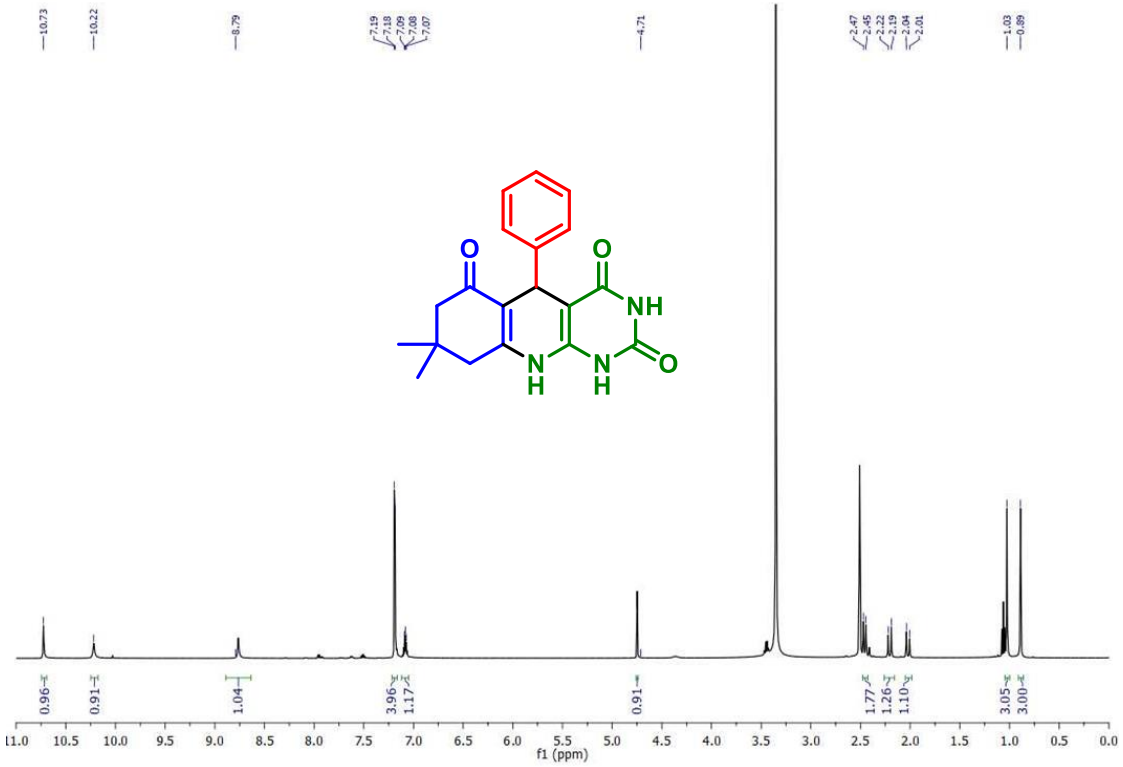


Figure 4.2 ^{1}H NMR of product **4a**

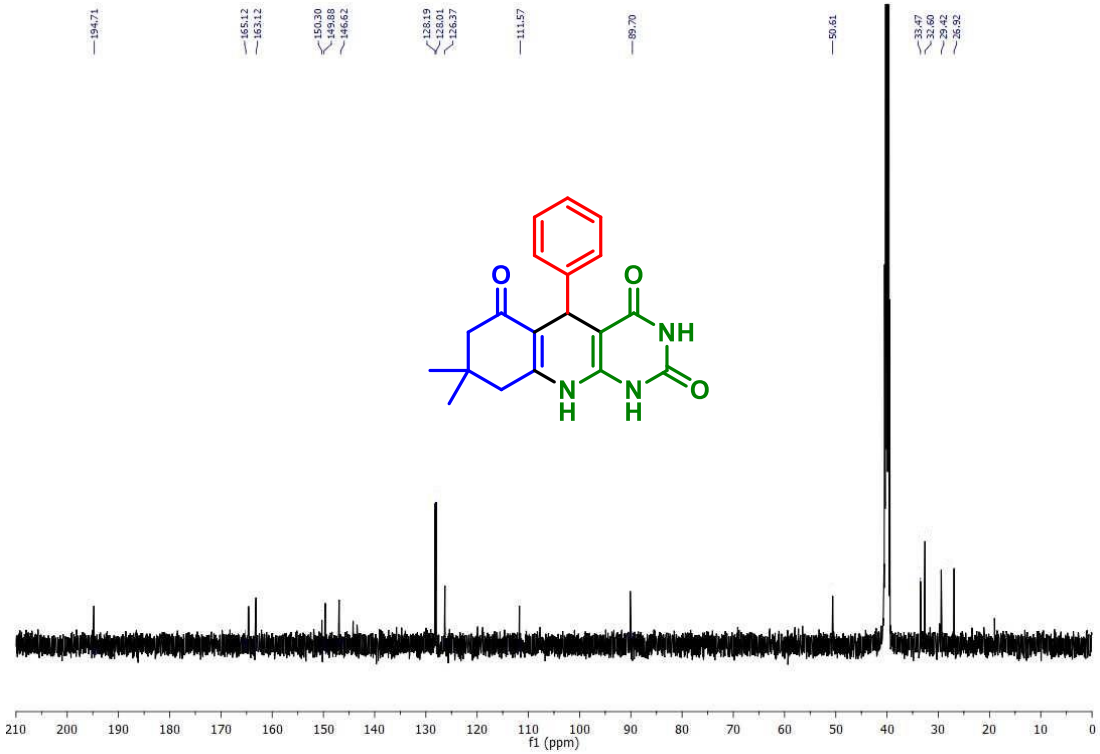


Figure 4.3 ^{13}CNMR of product **4a**

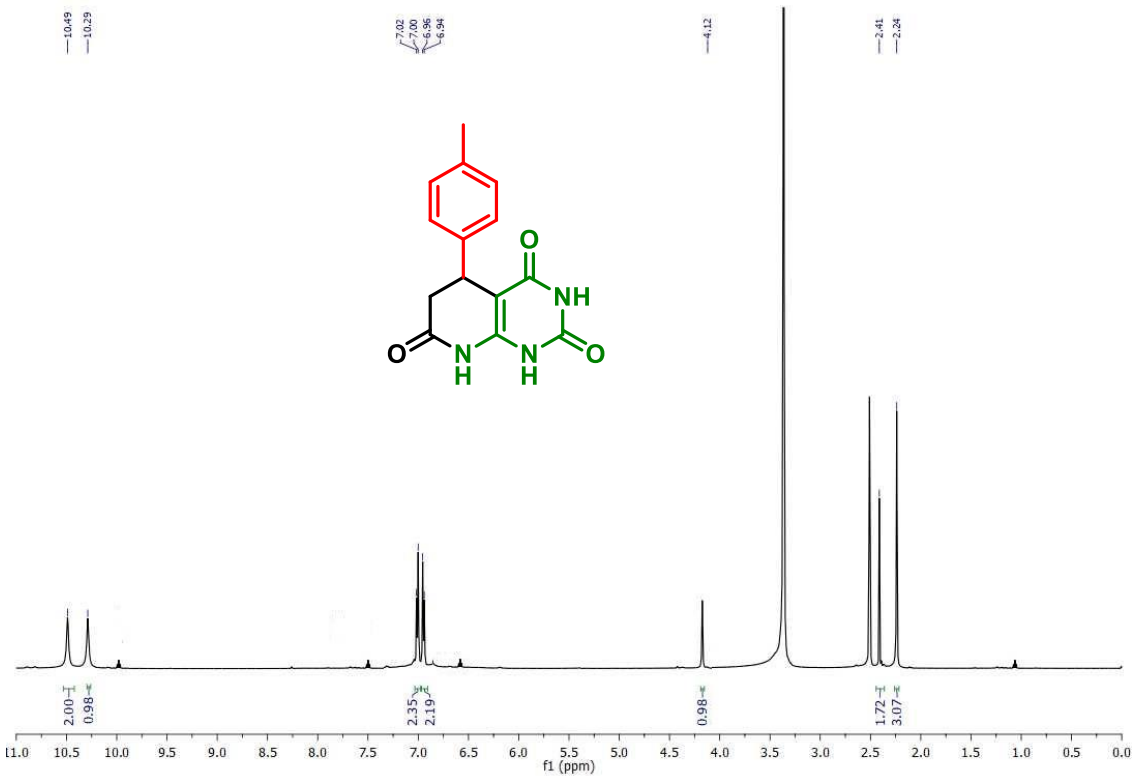


Figure 4.4 ^{1}H NMR of product **5c**

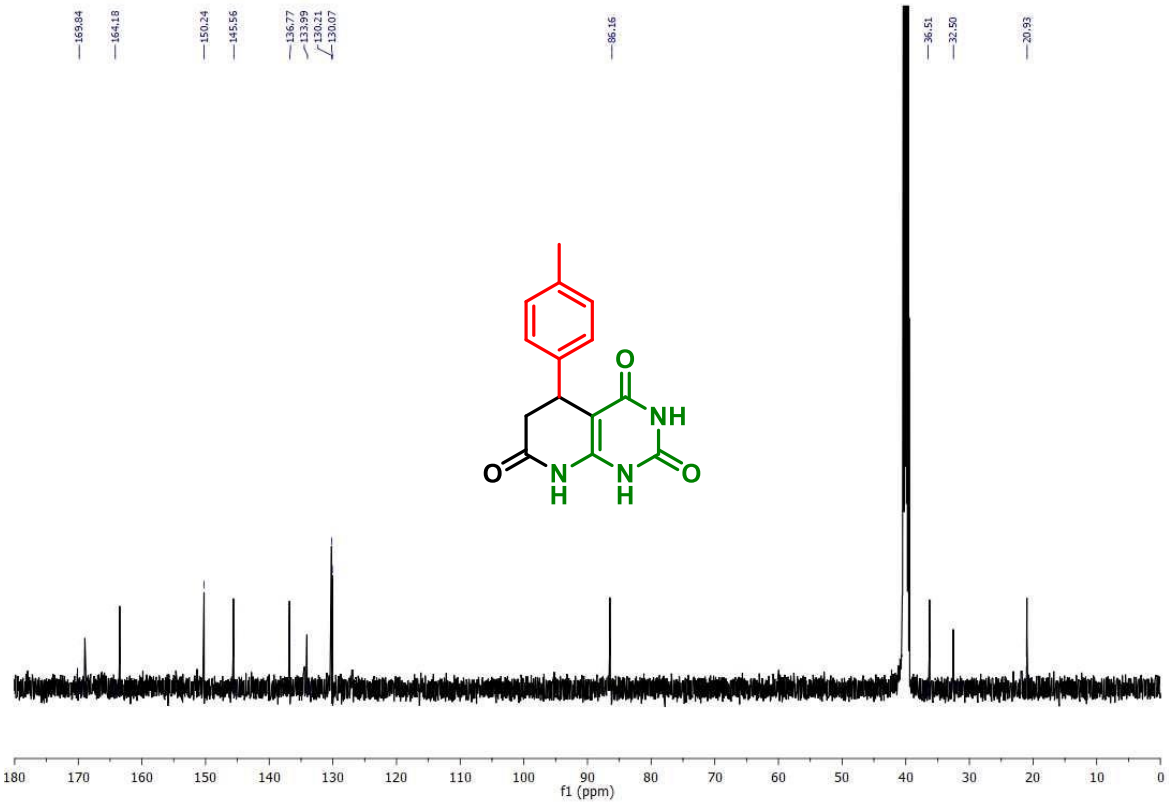


Figure 4.5 ^{13}C NMR of product **5c**

4.8 HRMS Spectra

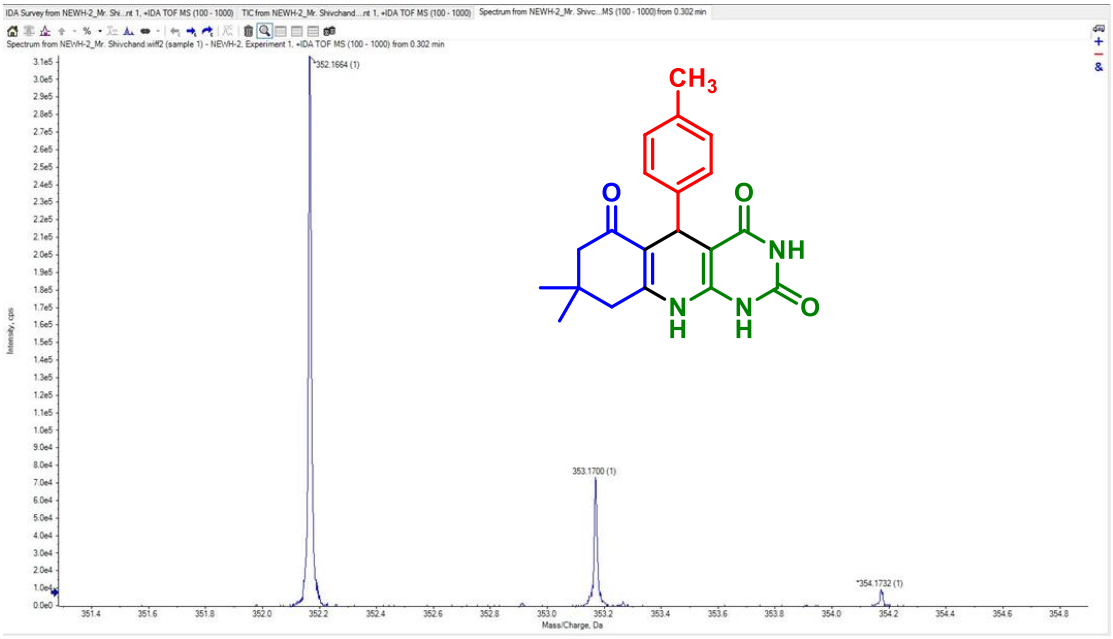


Figure 4.6 HRMS Spectra of **4b**

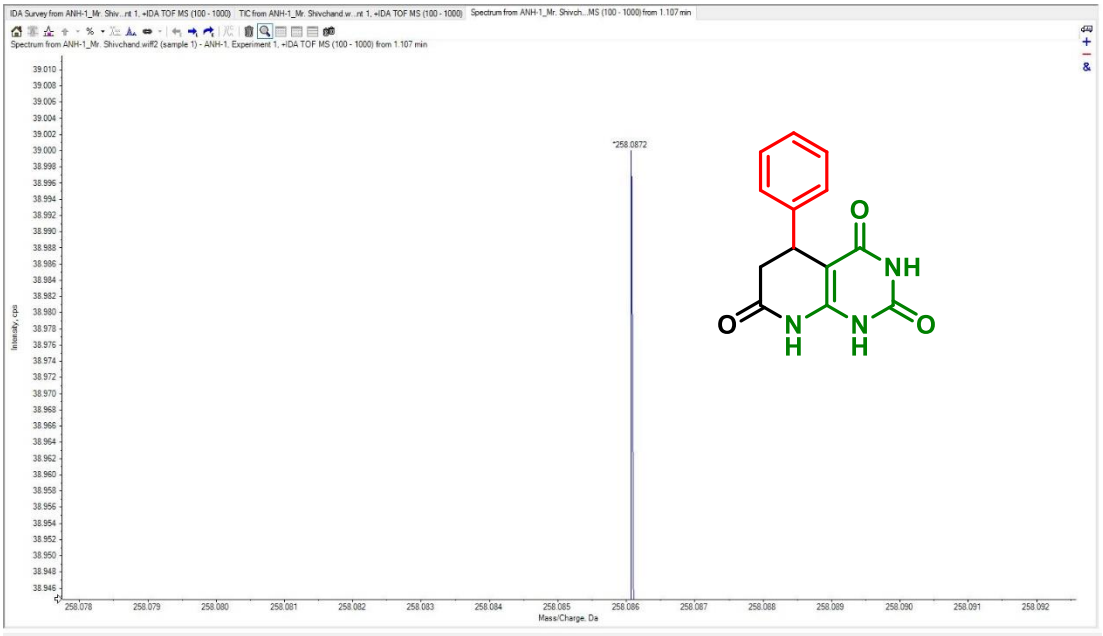


Figure 4.7 HRMS Spectra of **5a**

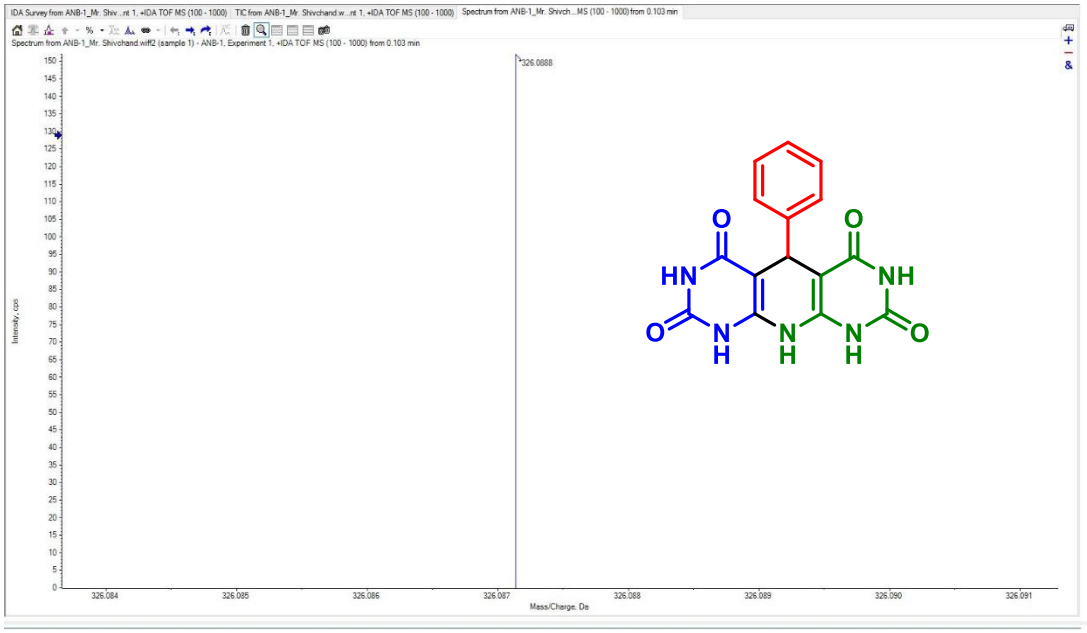


Figure 4.8 HRMS Spectra of **4l**

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