CHAPTER 3

"On-water" synthesis of heterocycles functionalised chromenopyrimidines from benzylidene barbiturates of 2-hydroxybenzaldehydes

3.1 INTRODUCTION

Heterocyclic compounds like pyrimidines and chromenes have been extensively utilized for the preparation of medicinal compounds and finds application for a wide spectrum of medical purposes. They have been used individually and in fused forms. Some noteworthy fused pyrimidines are pyrolo[2,3-*d*]pyrimidines, thieno[2,3-*d*]pyrimidines, pyrano[2,3-*d*]pyrimidines, chromeno[2,3-*d*]pyrimidines and pyrazolo[3,4-*d*]pyrimidines etc. Fused pyrimidine scaffolds have been an integral part of pharmaceutically active compounds showing inhibitory activities against diseases like influenza. They have been reported to act as antimicrobial agents, inhibitors of ABC transporters as well as metalloproteinase-10/13, and tauopathies and ABC1, ABCC1 and ABCG2 anatagonists [1-14]. Such promising activities of fused structures of pyrimidines call for the synthesis of new structures and exploration of the same in pharmaceutics so that the library of bioactive agents may expand.

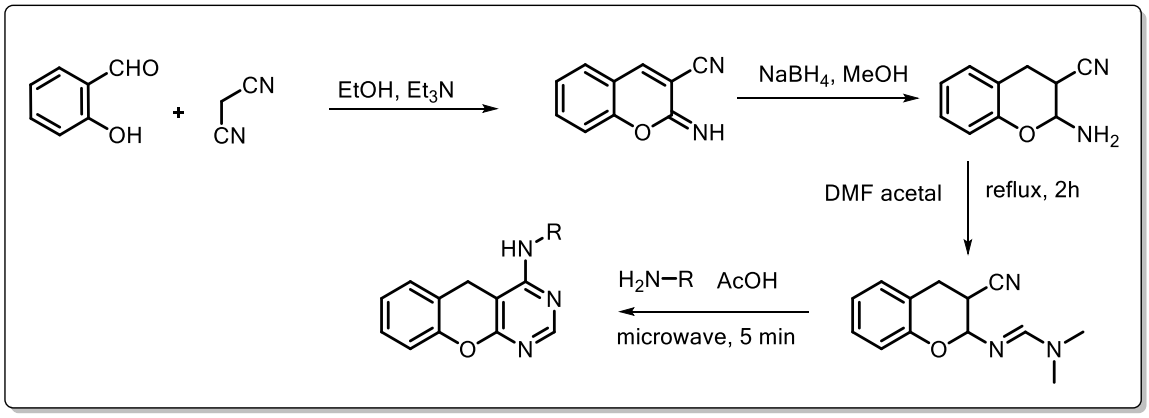
Similarly, derivatives of chromene heterocycles, which are widely present in plants and plant based edible products [15] and several bioactive natural products, have shown efficient disease preventing abilities [16]. Deriving inspirations from nature, the synthetic analogues of chromene derivatives have been popular in the pharmaceutical domains for quite some time now [17]. They have been used as antifungal [18], antimicrobial [19], molluscidial [20], anticoagulant, spasmolytic, diuretic, anti-tumour, and anti-naphylactic agents [21].

Chromenopyrimidines are a class of fused heterocycles which display remarkable therapeutic properties and are present in many drugs and natural products [22,

23]. The broad spectrum of potent biological activities [24-29] and disease preventing attributes [30] make it a privileged structural motif. Along with applications in biodegradable agro-chemicals [31], they are used in cosmetics and pigment industries too [32].

Our continued interests in pyrimidine based fused heterocycles have presented before us the multiutilitarian and highly prospective chromenopyrimidine heterocycles. Some noteworthy methods of synthesis of this skeleton are discussed in the following segment.

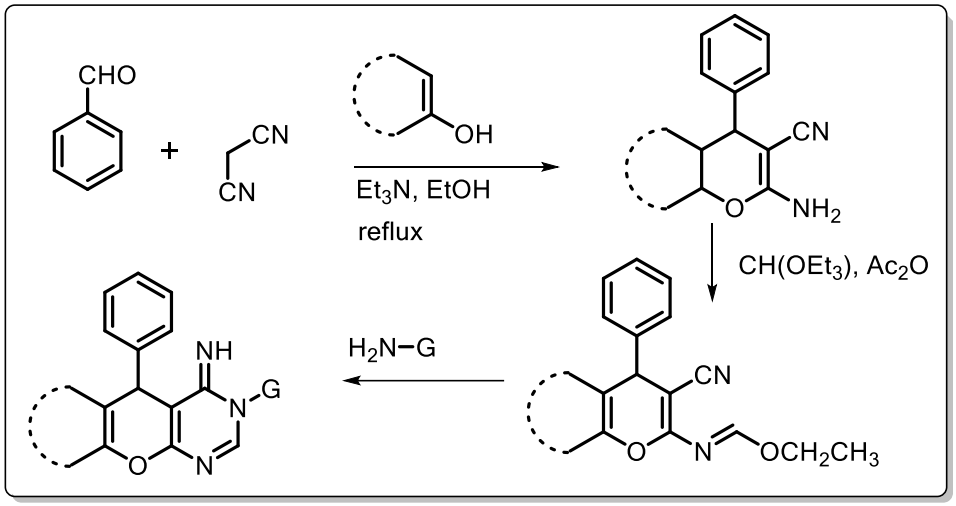
Rai *et al.* in 2010 reported an efficient microwave irradiated synthesis of chromeno[2,3-*d*]pyrimidine derivatives from the imine of 2-amino-3,4-dihydro-2*H*-chromene-3-carbonitriles by reacting with aniline in the presence of acetic acid. In the same report they showed the antimicrobial activity of the compounds formed (**scheme 3.1**) [33].



Scheme 3.1 Microwave irradiated synthesis of chromeno[2,3-*d*]pyrimidine derivatives (Rai *et al.*)

A very similar report was published by Mobinikhaledi *et al.* in 2014, where they showed a multistep synthesis of chromeno[2,3-*d*]pyrimidine by first forming 2-

amino-3,4-dihydro-2*H*-chromene-3-carbonitriles *via* a classical base mediated MCR strategy. This was the converted into an imine and further treated with ammonia derivative to form the chromenopyrimidine product (**scheme 3.2**) [34].

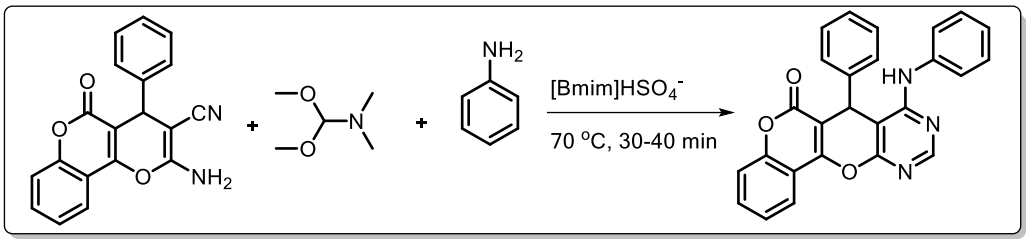


Scheme 3.2 Multistep synthesis of chromeno[2,3-*d*]pyrimidine (Mobinikhaledi *et al.*)

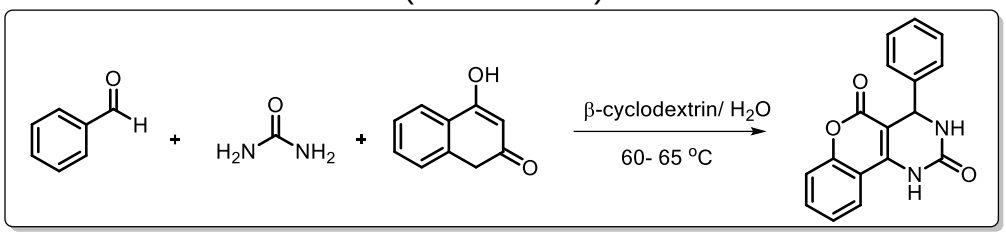
Suresh *et al.* in 2016 reported a greener protocol through an ionic liquid ([Bmim]HSO_4^-) mediated synthesis of chromenopyrano[2,3-*b*]pyrimidines from 2-amino-pyrano[2,3-*c*]-chromene-3-carbonitriles, *N,N*-dimethylformamide dimethyl acetal and aromatic amines. The synthesized products were successfully screened for antibacterial activities (**scheme 3.3**) [35].

Bhosle *et al.* in 2018 reported an MCR synthesis of chromenopyrimidines in aqueous β-cyclodextrin by reacting aromatic aldehyde, urea and 4-hydroxycoumarins (**scheme 3.4**) [36].

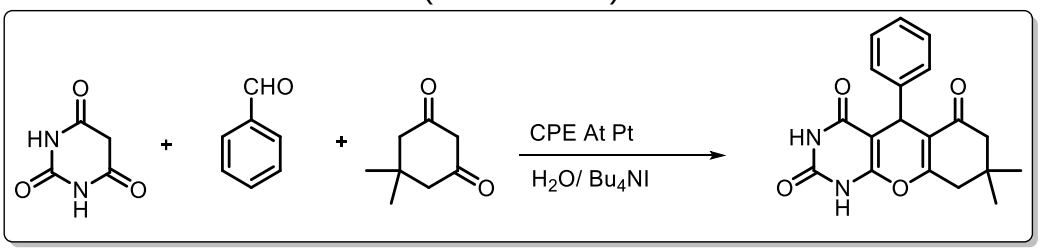
Malviya and Singh in 2019 reported an electrochemical approach for the synthesis of chromeno[2,3-*d*]pyrimidine derivatives *via* one-pot three component MCR strategy (**scheme 3.5**) [37].



Scheme 3.3 Ionic liquid mediated synthesis of chromenopyrano[2,3-*b*]pyrimidines (Suresh *et al.*)



Scheme 3.4 MCR synthesis of chromenopyrimidines in aqueous β-cyclodextrin (Bhosle *et al.*)

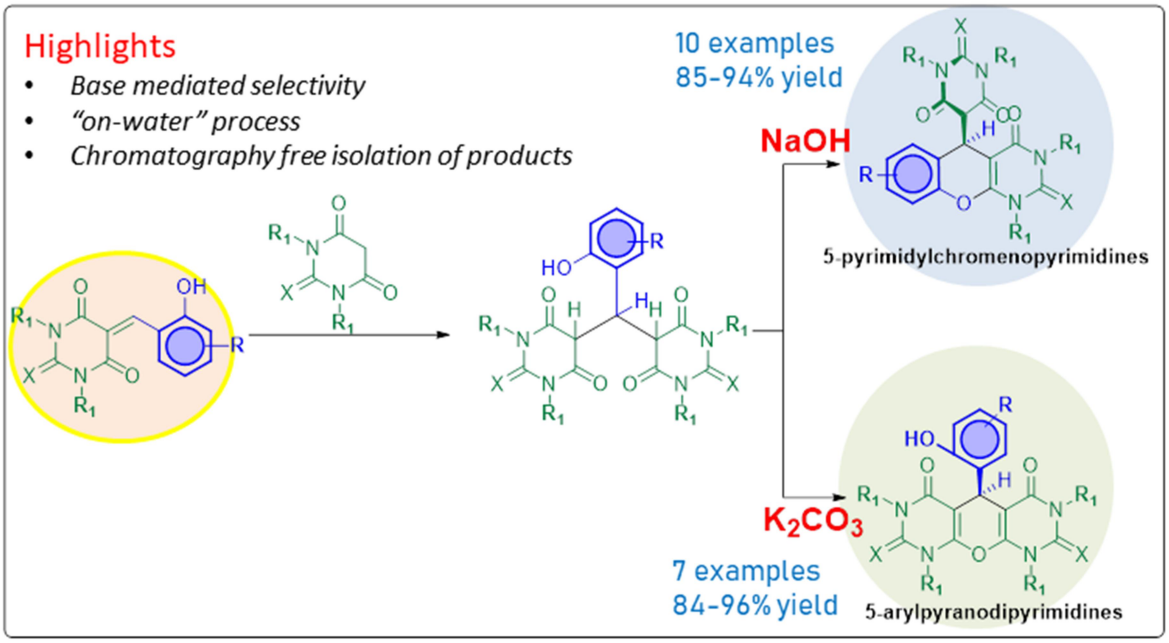


Scheme 3.5 Electrochemical synthesis of chromeno[2,3-*d*]pyrimidine derivatives (Malviya and Singh)

From the above reports we can deduce that chromenopyrimidine derivatives could be formed from some elemental heterocyclic structures and aldehydes. The biological activities of aryl substituted chromenopyrimidines are exemplary. So, if the aryl group is substituted with another active heterocycles, then the molecule may hold a higher prospect of being pharmaceuticaly active. In this chapter, we have tried to incorporate another heterocyclic ring to the chromenopyrimidines *via* MCR strategy and tried to accomplish the reactions on water. In the following sections we will see a base directed and an iodine-acetic acid catalysed synthesis of a library of functionalized adducts bearing the chromeno[2,3-*d*]pyrimidine scaffold.

Section 3.1

Base controlled selective synthesis of barbiturate functionalised chromeno[2,3-*d*]pyrimidines and 5-arylpyranodipyrimidines from benzylidene barbiturates of 2-hydroxybenzaldehydes



3.1.1 INTRODUCTION

The process of drug design is evolving day by day. Of late, the concept of molecular hybridization [38] has come up as a well-practiced process. Here, a bioactive compound is designed on the basis of recognizing the pharmacophoric subunits in different drug like candidates and then fusing them to form a new hybrid motif with extended pharmacological potential [39].

It has been a daunting task for modern day drug molecule designers to plan a sequence of highly efficient chemical reactions where a maximum could be achieved in terms of the assembling units bearing interesting properties [40, 41]. MCRs have emerged to be highly proficient tool in ticking all the boxes required to consider a reaction scheme facile, widely applicable, operationally simple, and which religiously follows the principles of green chemistry [42-50].

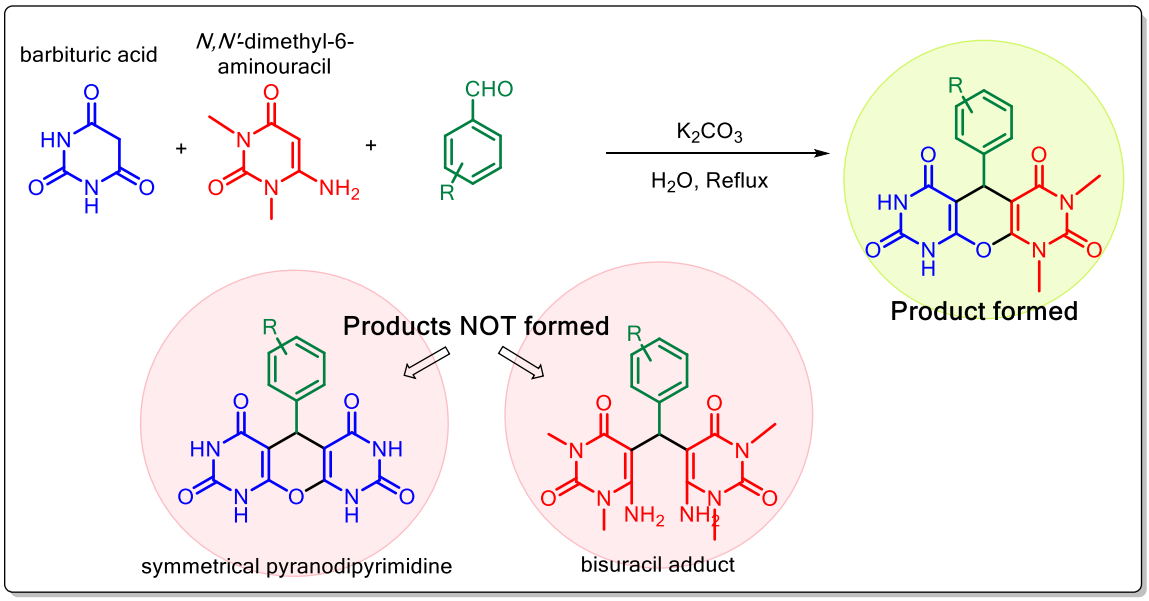
Barbiturates and chromenes are established biologically active scaffolds. Keeping in mind the objectives of molecular hybridization, we were excited to fuse them and further functionalizing them with another heterocyclic unit to construct a novel series of polyfunctionalised heterocyclic architecture. This being the main motive was also associated with the target of designing an MCR which satisfied the aspects of green chemistry.

As a part of our ongoing research in the field of on-water reactions with pyrimidines, herein we would like to illustrate a convenient, clean, and facile on-water method for the synthesis of barbituric acid functionalized chromeno[2,3-*d*]pyrimidines, from one pot MCR between barbituric acids and 2-hydroxybenzaldehydes. In the previous chapter, we have seen the formation of

unsymmetrical pyranodipyrimidines *via* two methods *viz*, base mediated and $FeCl_3 \cdot 6H_2O$ catalyzed routes. In this segment we will report an extended study of **section 2.1**, with 2-hydroxybenzaldehydes, which required a separate discussion due to some serendipitous outcomes.

3.1.2 RESULTS AND DISCUSSION

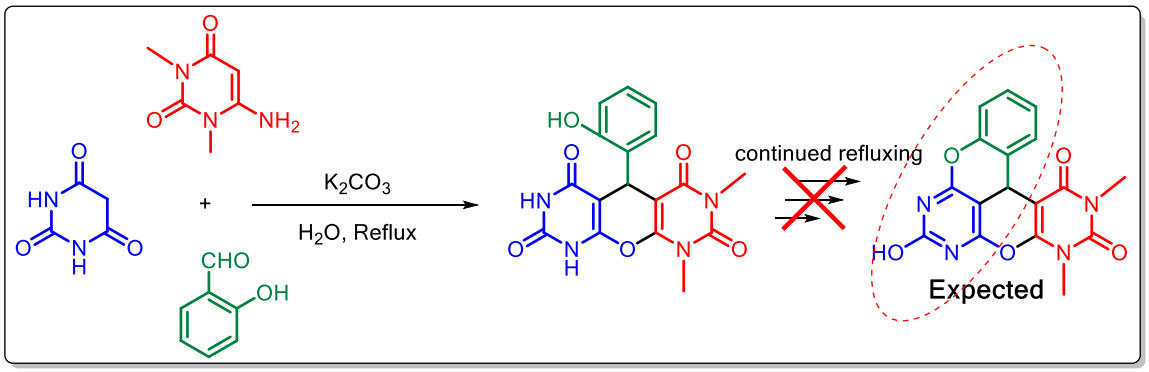
During the reaction between *N,N'*-dimethyl-6-aminouracil, aldehyde and barbituric acid, it was essential for us to monitor the formation of symmetrical pyranodipyrimidine products because there always existed a high probability of side reactions (**scheme 3.1.1**).



Scheme 3.1.1 Probable products of the MCR between *N,N'*-dimethyl-6-aminouracil, aldehyde and barbituric acid

Therefore, before moving onto spectroscopic and spectrometric methods of identifying the products, the TLC method was applied. As a reference is required for TLC, therefore we sought to carry out a separate reaction and synthesized the symmetrical pyranodipyrimidine adduct by refluxing 2 equivalents of barbituric

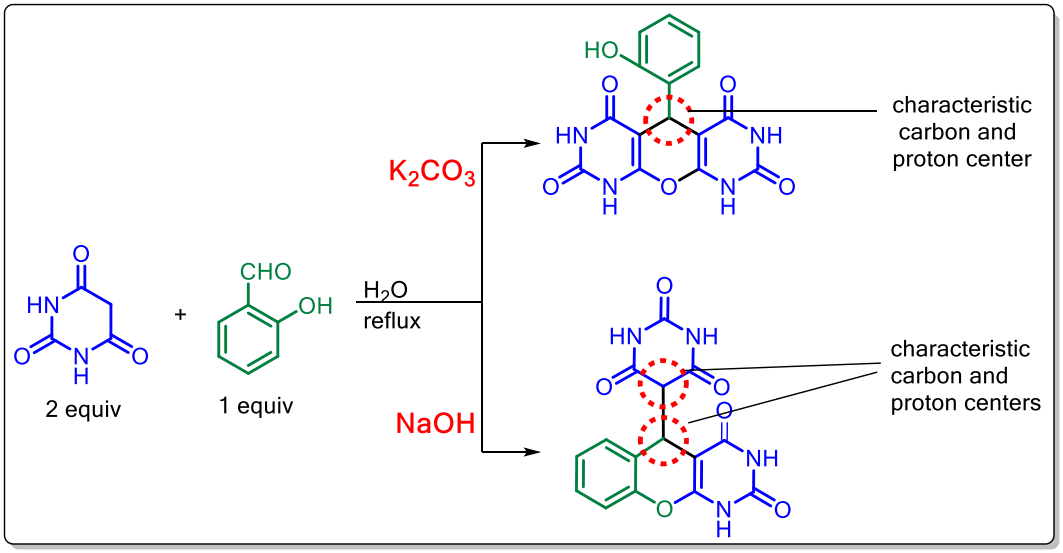
acid with 1 equivalent of the aromatic aldehyde in the presence of a base for 1 hour and filtering the product out. As mentioned in **section 2.1** that the symmetrical adduct was not formed by using the protocol discussed there. However, an interesting turn of events gave a direction to explore another route. The same reaction protocol was tried on 2-hydroxybenzaldehydes and the refluxing was continued for a prolonged period of time expecting the hydroxyl group of the aldehyde to further participate in the reaction and form a ring of its own (**Scheme 3.1.2**).



Scheme 3.1.2 Expected ring formation in unsymmetrical pyranodipyrimidines formed from 2-hydroxybenzaldehyde

Again to check whether the expected unsymmetrical pyranodipyrimidine was formed or not, the reference compounds (i.e. symmetrical pyranodipyrimdine from barbituric acid and the bis uracil from 6-aminouracil unit) were prepared. When the reaction for the preparation of the reference compounds was carried out in the presence of NaOH instead of K_2CO_3, the resultant symmetrical pyranodipyrimidine was not formed. It was indicated by the unexpected change in colour of the product formed. When it was compared with the product formed with K_2CO_3, and then it was discovered to be different. This should not have been the case because for all other aldehydes, the base did not play a major role in

determining the selectivity of the product and gave the same results. This NaOH mediated reaction product was isolated *via* filtration and washed with DCM, ethanol and water. Following this, it was dried and then characterized with the help of ^{1}H and ^{13}C NMR spectroscopy. The presence of two adjacent –CH proton peaks showing doublets, absence of –OH proton peak, and the presence of three –NH proton peaks in the ^{1}H NMR spectra, and the presence of two tertiary methyl carbons and four carbonyl groups in the ^{13}C NMR spectra indicated the presence of two barbiturate groups, of which one had not participated in the ring formation, and the utilization of the hydroxyl group of the aldehyde in ring formation. From these observations we could deduce that the product formed in the NaOH mediated reaction was a chromenopyrimidine adduct with an attached barbiturate group, while the product formed *via* K_2CO_3 mediated reaction was a symmetrical pyranopyrimidine. The summary of the observations is shown in **scheme 3.1.3**.



Scheme 3.1.3 Comparative study between NaOH and K_2CO_3 mediated synthesis of chromenopyrimidine and pyranodipyrimidine from the same starting substrates

These preliminary observations instigated us to explore the sodium hydroxide mediated synthesis of barbiturate functionalised chromenopyrimidines. Consequently, we began our study by studying the reaction between 1,3-dimethylbarbituric acid (2 mmol) and 2-hydroxybenzaldehyde (1 mmol), which was mediated by NaOH (1 mL of 1 M solution i.e., 1 mmol) in water. The reaction mixture was refluxed for 1 hour and the resultant solid product was isolated by filtration. The isolated product was washed with DCM, ethanol and water, followed by drying in vacuum. This was then characterised by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The characteristic –CH tertiary methyl proton peaks of the chromene ring and the barbiturate group which was a substituent on the chromenopyrimidine moiety showed resonance as doublets at δ 5.11 ppm and 4.10 ppm. In ^{13}C NMR, both the tertiary methyl –CH carbons showed resonance at δ 36.3 ppm and 54.3 ppm (**figure 3.1.1**). The mass spectrum showed a molecular ion peak at m/z $(M+H)^+$ 398.1241, which correlated with its molecular formula: $C_{19}H_{18}N_4O_6$. This confirmed that the compound formed was 5-(1,3-dimethyl-2,4-dioxo-1,3,4,4a,5,10a-hexahydro-2*H*-**chromeno[2,3-*d*]pyrimidin-5-yl)**-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione

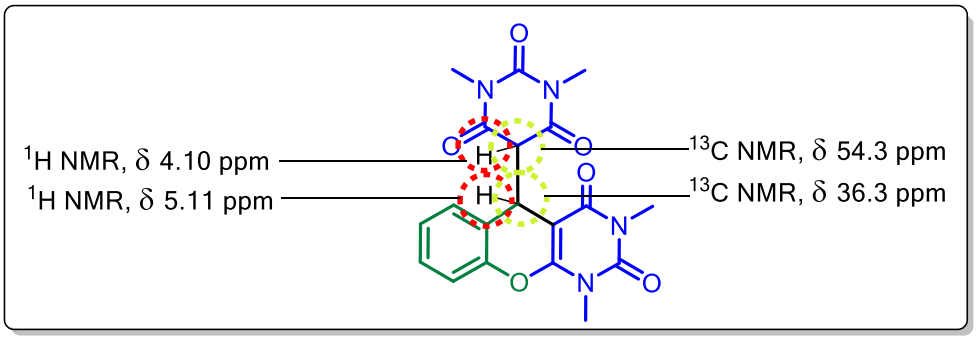
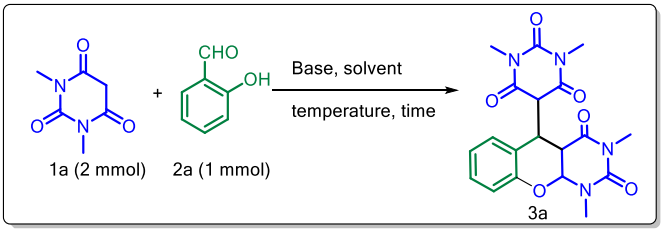


Figure 3.1.1 Assignment of ^{1}H and ^{13}C NMR signals to barbiturate functionalised chromeno[2,3-*d*]pyrimidine

Following this, the optimisation of the reaction was carried out. It was found that the optimum amount of base required for the reaction was 1 mmol. The best activity was shown by strong bases such as KOH, NaOH and Cs_2CO_3. However, from the economic point of view, NaOH was preferred. Some common solvents were screened to check if any change in the course of the reaction occurred because of solvent polarity or protic and aprotic nature. The results showed that a polar protic environment is required of the reaction to take place. Some polar aprotic solvents were also successful in mediating the reaction but, the yields were compromised. Also, isolation of the product from high boiling polar aprotic solvents, like DMSO, proved to be a tedious task. Temperature was an essentiality and the reaction was feasible only under refluxing conditions. Lower temperature resulted in decrease of yields and the reaction did not proceed beyond the formation of benzylidene barbiturates at room temperature. The optimisation study is summarised in **table 3.1.1**.

Table 3.1.1 Optimisation of the reaction

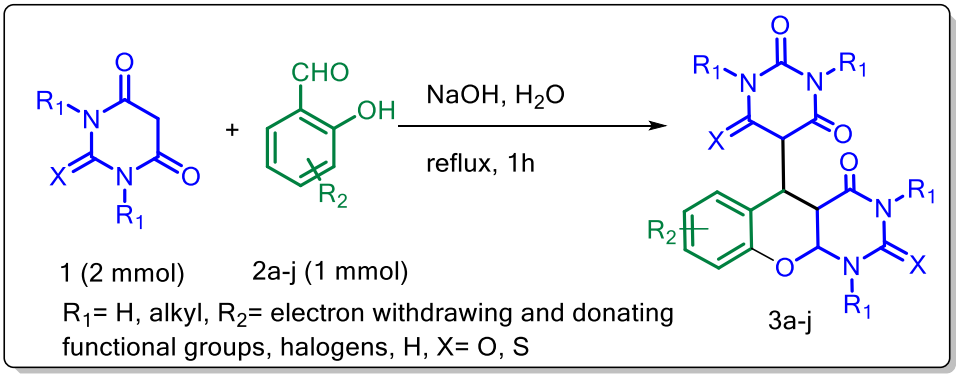


Entry	Base (mmol)	Solvent (5 mL)	Temperature (˚C)	Time (h)	Isolated Yield %
1[a]	NaOH (1)	H_2O	reflux	1	92
2	NaOH (1.5)	H_2O	reflux	1	92
3	NaOH (0.5)	H_2O	reflux	1	68
4	KOH (1)	H_2O	reflux	1	92
5	NH_4OH (1)	H_2O	reflux	1	nr[b]

6	Cs_2CO_3 (1)	H_2O	reflux	1	92
7	K_2CO_3 (1)	H_2O	reflux	1	nr[b]
8	Et_3N (1)	H_2O	reflux	1	nr[c]
9	No base	H_2O	reflux	1	nr[c]
10	NaOH (1)	H_2O	130	1	92
11	NaOH (1)	H_2O	70	2	72
12	NaOH (1)	H_2O	rt (28)	6	nr[c]
13	NaOH (1)	H_2O	reflux	1.5	92
14	NaOH (1)	H_2O	reflux	30 min	68
15	NaOH (1)	H_2O	reflux	15 min	46
16	NaOH (1)	H_2O:EtOH (1:1)	reflux	1	92
17	NaOH (1)	ETOH	reflux	1	90
18	NaOH (1)	CH_3CN	reflux	1	26
19	NaOH (1)	DMSO	reflux	1	84
20	NaOH (1)	DMF	reflux	1	traces
21	NaOH (1)	DCE	reflux	1	nr[d]
22	NaOH (1)	Toluene	reflux	1	nr[d]

Reaction conditions: *N,N'*-dimethylbarbituric acid (2 mmol, 0.156 g) and 2-hydroxybenzaldehyde (1 mmol, 0.122 g), base, solvent, temperature, time. [a]Best reaction conditions; [b]symmetrical pyranodipyrimidine was formed; [c]reaction halted at the benzylidene barbiturate state; [d]trace amount of benzylidene barbiturates were formed.

From the optimisation of the reaction conditions we arrived at the optimised reaction scheme (**scheme 3.1.4**).

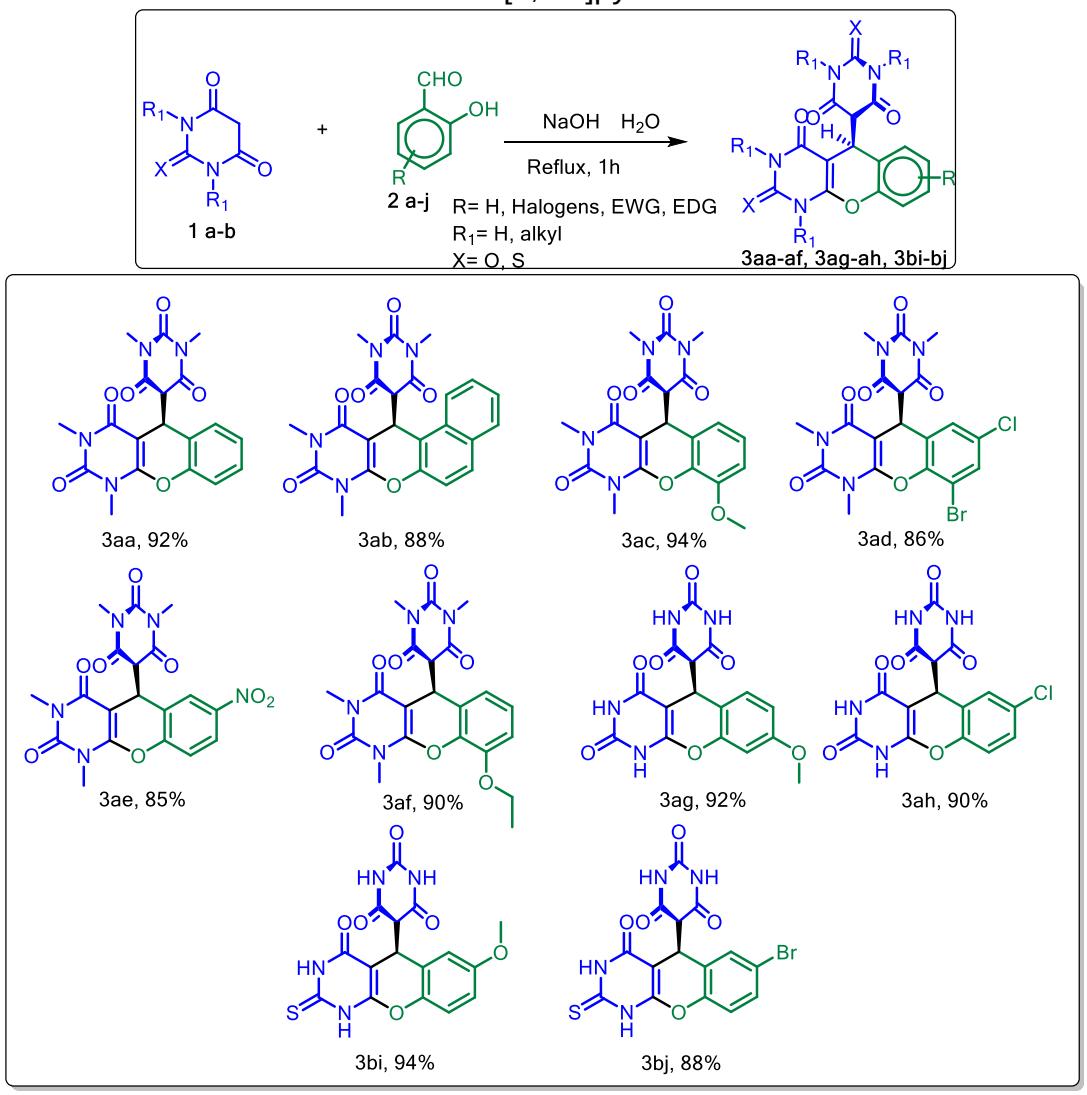


Scheme 3.1.4 Optimised scheme for the base mediated synthesis of barbiturate functionalised chromeno[2,3-*d*]pyrimidine.

This optimised reaction protocol was extended towards the synthesis of a library of barbiturate substituted chromeno[2,3-*d*]pyrimidines (**scheme 3.1.5**) and the

effect of different substituents was studied. The presence of electron donating groups on the 2-hydroxyaldehydes favoured the reaction, by increasing the nucleophilicity of the probable phenoxide ion formed and thereby accelerated the formation of the chromene ring. Electron withdrawing groups, on the other hand resulted in slight decrease in the yields of the product. No remarkable effect of steric crowd was observed. Again, the reaction was also carried out with 2-hydroxy-aromatic ketones, but desirable results were not obtained.

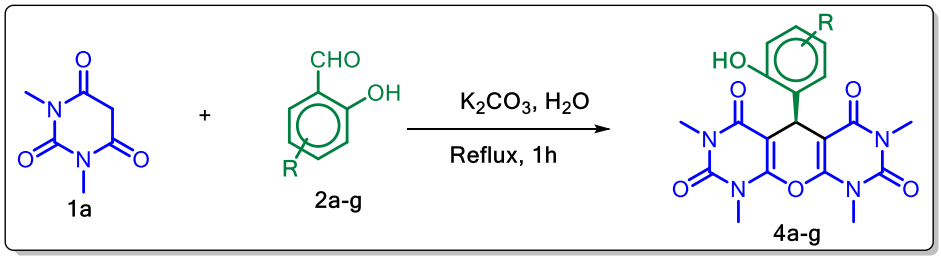
Scheme 3.1.5 Substrate study for base mediated synthesis of barbiturate functionalised chromeno[2,3-*d*]pyrimidines.

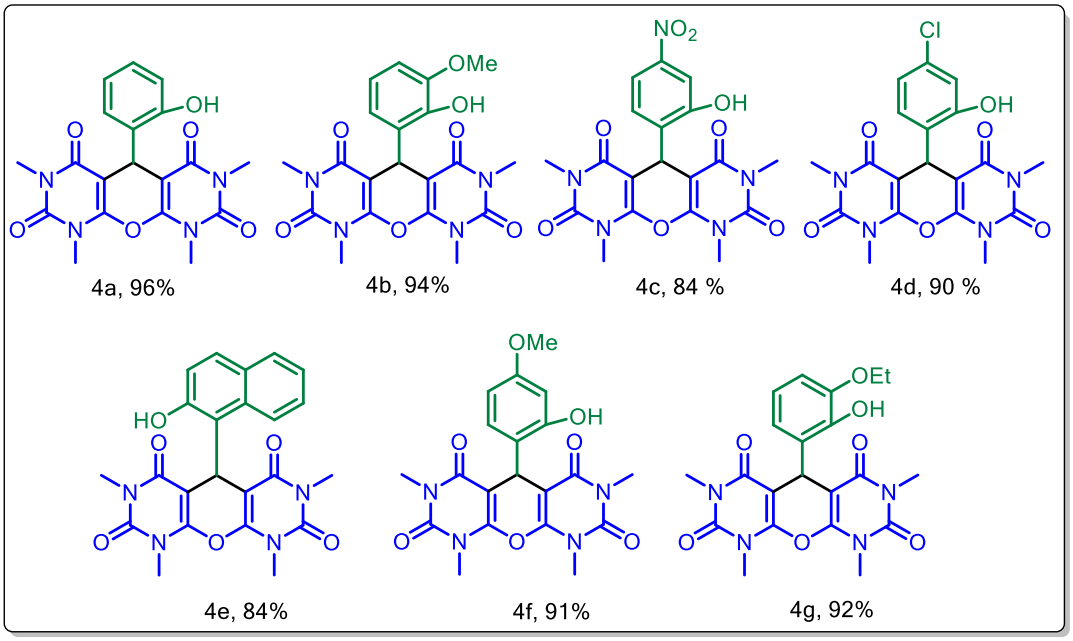


Reaction conditions: barbituric acid (2 mmol) and 2-hydroxybenzaldehydes (1 mmol), NaOH (1 mmol), H_2O (5 mL), reflux, 1h

Since, it was also observed that in the presence of a mild base like K_2CO_3 the reaction proceeds towards the formation of symmetrical pyranodipyrimidines, the scope of study was also extended towards exploring the formation of this class of compounds (**scheme 3.1.6**). The motive behind doing so was to showcase the selective activation of hydroxyl groups towards the formation of two different types of pyran rings in the presence of two different bases of varied strength. While a strong base resulted in the activation of the phenolic –OH followed by cyclisation through the carbonyl group of the barbiturate moiety, the weaker base caused condensation between the two barbiturate groups alone.

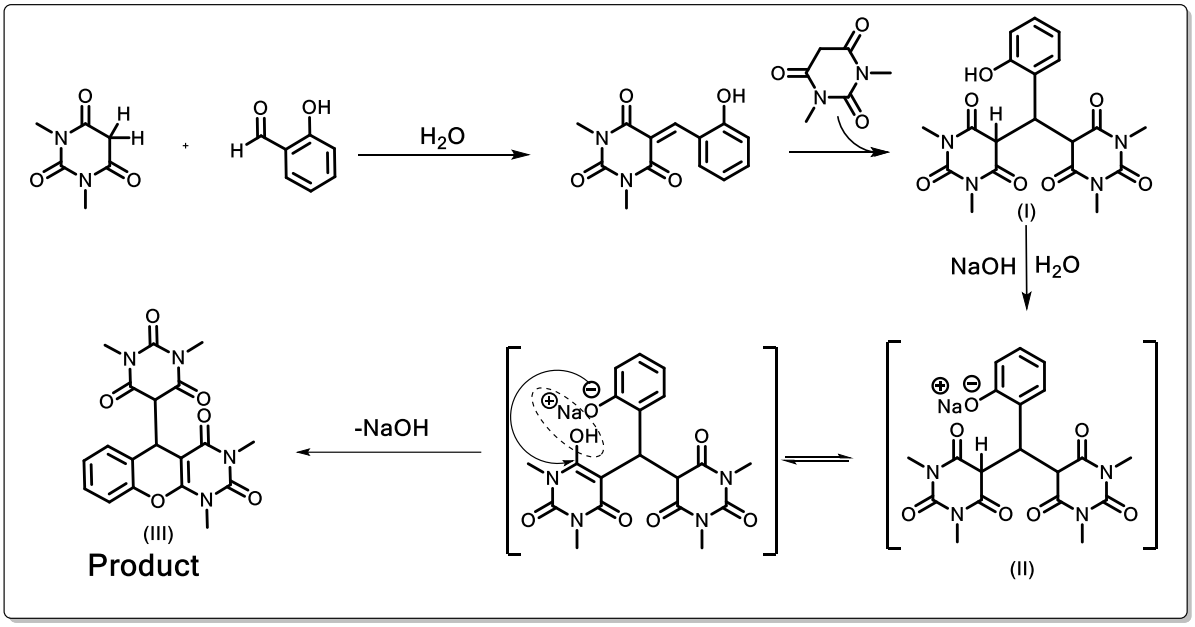
Scheme 3.1.6 Substrate study for base mediated synthesis of symmetrical pyranodipyrimidines





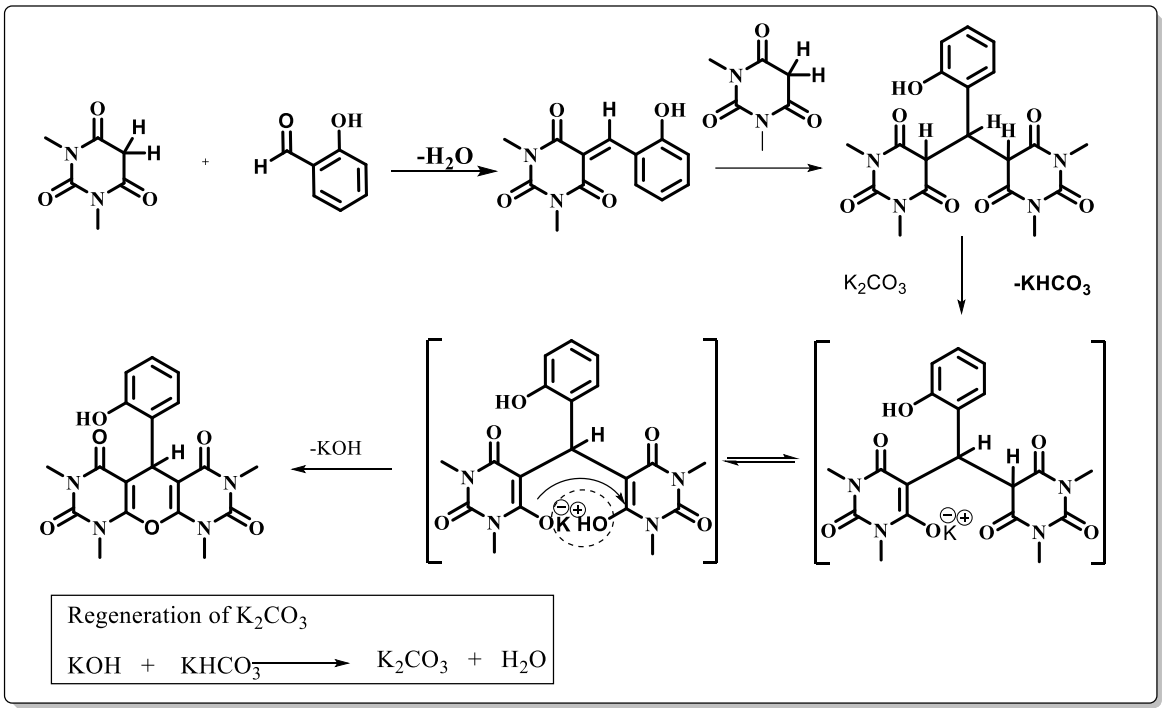
Reaction conditions: barbituric acid (2 mmol) and 2-hydroxybenzaldehydes (1 mmol), K_2CO_3 (1 mmol), H_2O (5 mL), reflux, 1h

The plausible mechanism of the NaOH mediated synthesis of barbiturate functionalised chromeno[2,3-*d*]pyrimidines can be carried forward from the Knoevenagel condensation of the 2-hydroxybenzaldehyde and barbituric acid. The resultant benzylidene barbiturate undergoes a Michael addition with another barbituric acid to form a bisbarbiturate adduct (I). The 2-hydroxy group of the aryl part undergoes dehydrogenation in the presence of a strong base like NaOH and forms the phenoxide ion (II), which further undergoes cyclisation with the carbonyl group of one of the barbiturate part to form the chromene ring (III) (**scheme 3.1.7**).



Scheme 3.1.7 Plausible mechanism for the formation of barbiturate functionalised chromeno[2,3-*d*] pyrimidines

In the presence of a mild base like K_2CO_3, the formation of phenoxide ion does not take place and a condensation step takes place between the two carbonyl groups of the barbiturate segments. This results in the formation of symmetrical pyranodipyrimidines instead (**scheme 3.1.8**).



Scheme 3.1.8 Plausible mechanism for the formation of symmetrical pyranodipyrimidines

It can be said that the same reactants performed differently in the presence of two bases with different strength. The yields in both the cases were satisfactorily good. Also, no side products were formed and the compounds isolated were of high purity

3.1.3 EXPERIMENTAL SECTION

General Information

All reagents were purchased from commercial sources and used as received, without any purification. Commercially available solvents were distilled before the reactions and water used for reaction as well as during work up was double distilled prior to use. ^{1}H and ^{13}C NMR spectra of the products were recorded with a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using deuterated dimethyl

sulphoxide (DMSO-D_6, δ= 2.46ppm, quintet, for ^{1}H and 40.0 ppm, septet, for ^{13}C) as the solvent as well as the internal standard and deuterated chloroform ($CDCl_3$) as the solvent and Tetramethylsilane (TMS) as the internal standard. Additional signal at 3.30 ppm, in ^{1}H NMR spectra, is seen because of the presence of HOD in DMSO-D_6. Similarly, due to the presence of HOD in $CDCl_3$ an additional signal at 1.59 ppm is observed in the ^{1}H spectrum. Chemical shift values are expressed in ppm. Coupling constants (*J*) are expressed in Hertz (Hz). The signals are reported as “s”= singlet, “d”= doublet, “t”= triplet, and “m”= multiplet. HRMS data were recorded by electrospray ionization with a Q-TOF mass analyzer. Reactions were monitored by thin-layer chromatography using aluminium sheets with silica gel 60F_{254} (Merck). UV light and Iodine vapors were used as visualizer.

General Procedure for the synthesis of 5-(2,4-dioxo-1,3,4,4a,5,10a-hexahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (barbiturate functionalised chromeno[2,3-*d*]pyrimidine) (3aa-ah, 3bi, 3bj)

In a round bottomed flask, Barbituric acid or Thiobarbituric acid (2 equiv), 2-hydroxybenzaldehyde (1 equiv) and sodium hydroxide (1 equiv) was added to form a slurry with 5 mL distilled H_2O. A Graham condenser was fitted to the reaction vessel. Following this stirring was continued under reflux at 100 °C for 1 hour. The initial slurry formed turns into a clear solution. After the completion of the reaction, as indicated by the appearance of precipitate and also by thin layer chromatography, the reaction mixture was cooled and filtered off. The precipitate was washed with water, ethanol and dichloromethane and dried under vacuum. It was then characterized without further purification.

General Procedure for the synthesis of 5-(2-hydroxyphenyl)-1,3,7,9-tetramethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraones (symmetrical pyranodipyrimidines) (4a-g)

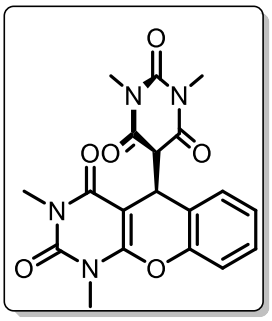
In a round bottomed flask, *N,N'*-dimethylbarbituric acid (2 equiv), 2-hydroxybenzaldehyde (1 equiv) was added to form a slurry with 5 mL distilled H_2O. After this, K_2CO_3 (1 equiv) was added to the mixture and a Graham condenser was fitted to the reaction vessel. Following this stirring was continued under reflux at 100 °C for 1 hour. After the completion of the reaction, as indicated by the appearance of precipitate and by thin layer chromatography, the reaction mixture was cooled and filtered off. The precipitate was washed with water, ethanol and dichloromethane and dried under vacuum. It was then characterized without further purification.

3.1.4 CONCLUSION

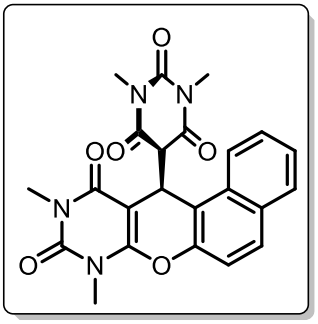
In conclusion, it can be stated that base mediated selective synthesis of 5-(2,4-dioxo-1,3,4,4a,5,10a-hexahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones (barbiturate functionalised chromeno[2,3-*d*]pyrimidine) and 5-(2-hydroxyphenyl)-1,3,7,9-tetramethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraones (symmetrical pyranodipyrimidines) was achieved through simple yet highly efficient methods. The mechanisms were explained in lines of the data available in literature and basic organic principles. The selectivity of the two processes, under the given conditions, was satisfactorily high and the products isolated were of high purity. Moreover, the products were isolated *via* simple filtration and required no chromatographic method of purification. Additionally, the methods developed were green,

operationally simple and safe. The target of developing “on-water” protocols for the synthesis of fused pyrimidine scaffolds was successfully accomplished.

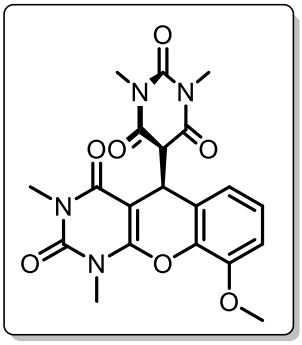
3.1.5 CHARACTERISATION DATA OF THE PRODUCTS



5-(1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3aa)
Deep yellow solid (366.20 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.34-7.26 (m, 1H), 7.19-7.06 (m, 3H), 5.11 (d, *J*= 2.5 Hz, 1H), 4.10 (d, *J*= 2.5 Hz, 1H **),** 3.53 (s, 3H), 3.34 (s, 3H), 3.25 (s, 3H), 3.05 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 167.2, 162.1, 154.7, 151.3, 150.7, 149.8, 129.6, 127.9, 126.2, 120.3, 116.9, 86.3, 54.3, 36.3, 29.3, 28.6, 28.2. **HRMS (+ESI)** calcd. for $C_{19}H_{18}N_4O_6$ $(M+H)^+$: 398.1226 found*:* 398.1235

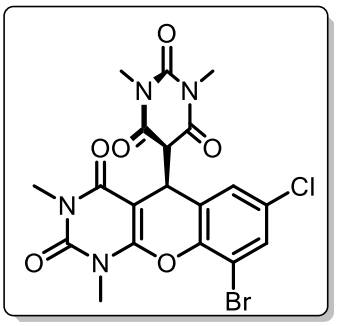


5-(8,10-dimethyl-9,11-dioxo-8,10,11,12-tetrahydro-9*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidin-12-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3ab)
Orange solid (394.50 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 8.21-8.24 (m, 1H), 7.77-7.81 (m, 1H), 7.58 – 7.41 (m, 3H), 7.35-7.39 (m, 1H), 5.06 (d, *J*= 2.5 Hz, 1H), 3.99 (d, *J*= 2.5 Hz, 1H), 3.43 (s, 3H), 3.26 (s, 3H), 2.97 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 168.8, 163.5, 154.1, 152.0, 149.3, 147.7, 133.6, 131.5, 128.4, 126.9, 125.3, 125.1, 119.5, 116.7, 102.2, 60.0, 35.2, 30.6, 28.6, 27.5. **HRMS (+ESI)** calcd. for $C_{23}H_{20}N_4O_6$ $(M+H)^+$: 448.1383 found*:* 448.1389



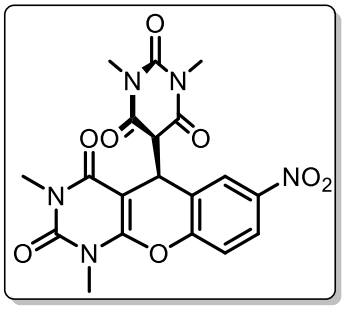
5-(9-methoxy-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3ac)

Yellow solid (401.98 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.29 (s, 1H), 6.97 (s, 1H), 6.83 (s, 1H), 5.15 (d, *J*= 2.2 Hz, 1H), 4.09 (d, *J*= 2.2 Hz, 1H), 3.85-3.89 (m, 3H), 3.54 (s, 3H), 3.27 (s, 3H), 3.02 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 168.5, 162.3, 157.0, 154.8, 144.3, 142.5, 137.3, 123.8, 122.6, 119.2, 117.3, 101.0, 69.7, 59.7, 36.9, 32.1, 30.8, 29.7. **HRMS (+ESI)** calcd. For $C_{20}H_{20}N_4O_7$ $(M+H)^+$: 428.1332 found*:* 428.1349



5-(9-bromo-7-chloro-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3ad)

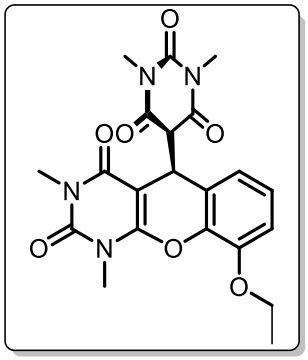
Pale yellow solid (437.74 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.68 (s, 1H), 7.54 (s, 1H), 5.27 (d, *J*= 2.5 Hz, 1H), 4.35 (d, *J*= 2.5 Hz, 1H), 3.44 (s, 3H), 3.12 (s, 3H), 2.97 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 164.0, 162.3, 158.02, 155.2, 149.5, 145.1, 136.0, 132.2, 131.9, 129.5, 119.0, 104.8, 62.7, 38.4, 33.4, 30.6, 28.7. **HRMS (+ESI)** calcd. for $C_{19}H_{16}BrClN_4O_6$ $(M+H)^+$: 509.9942 found*:* 509.9956



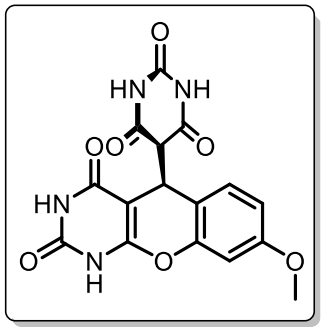
5-(1,3-dimethyl-7-nitro-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3ae)

Deep yellow solid (376.42 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 8.54 (s, 1H), 8.00 (d, *J*= 8.2 Hz, 1H), 7.46 (d, *J*= 7.8 Hz, 1H), 5.06 (d, *J*= 2.0 Hz, 1H), 4.12 (d, *J*= 2.0 Hz, 1H), 3.33 (s, 3H), 3.16 (s, 3H), 2.94 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 167.0,

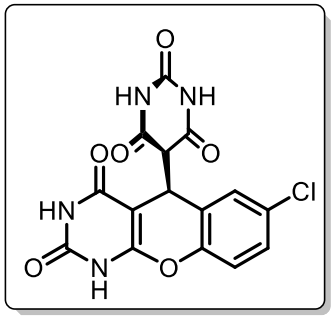
162.3, 158.2, 155.2, 153.2, 149.3, 147.1, 129.0, 127.2, 121.1, 118.3, 104.7, 59.6, 39.2, 32.4, 30.6, 29.7. **HRMS (+ESI)** calcd. for $C_{19}H_{17}N_5O_8$ $(M+H)^+$: 443.1077 found*:* 443.1091



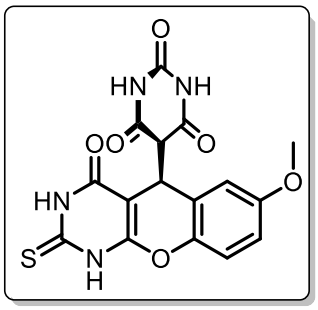
5-(9-ethoxy-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3af) Pale yellow solid (398.01 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.59-7.46 (m, 3H), 5.01 (d, *J*= 2.5 Hz, 1H), 4.49 – 4.41 (m, 3H), 3.31 (s, 3H), 3.27 (s, 3H), 2.92 (s, 6H), 1.53 (d, *J*= 2.5 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 169.0, 164.7, 158.0, 154.8, 152.5, 149.4, 143.2, 129.9, 127.2, 124.1, 122.0, 103.0, 66.2, 61.7, 38.9, 35.1, 31.6, 28.17, 17.2. **HRMS (+ESI)** calcd. for $C_{21}H_{22}N_4O_7$ $(M+H)^+$: 442.1488 found*:* 442.1505



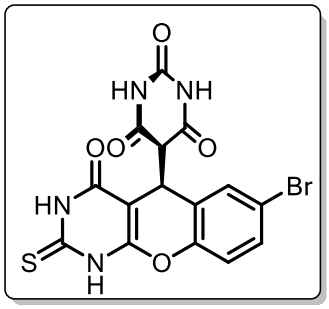
5-(8-methoxy-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3ag) Pale yellow solid (342.41 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 10.48 (s, 1H), 10.11 (s, 1H), 9.89 (s, 1H), 9.88 (s,1H), 8.15 – 8.11 (m, 2H), 7.64 (s, 1H), 5.14 (d, *J*= 2.5 Hz, 1H), 4.26 (d, *J*= 2.5 Hz, 1H), 3.92 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 174.2, 160.1, 159.8, 151.3, 150.6, 149.9, 140.7, 130.0, 114.3, 112.9, 104.8, 91.4, 56.4, 52.7, 36.9. **HRMS (+ESI)** calcd. for $C_{16}H_{12}N_4O_7$ $(M+H)^+$: 372.0706 found*:* 372.0717



5-(7-chloro-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3ah) Yellow solid (338.45 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 10.46 (s, 1H), 10.13 (s, 1H), 9.78 (s, br, 2H), 8.25 – 8.21 (m, 2H), 7.68 (s, 1H), 5.64 (d, *J*= 2.5 Hz, 1H), 4.54 (d, *J*= 2.5 Hz, 1H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 174.8, 164.4, 154.6, 153.3, 149.2, 144.8, 136.2, 132.3, 129.8, 121.1, 98.1, 56.9, 42.4. **HRMS (+ESI)** calcd. for $C_{15}H_9ClN_4O_6$ $(M+H)^+$: 376.0211 found*:* 376.0219

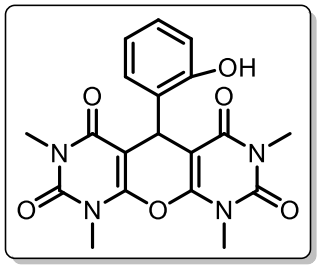


5-(7-methoxy-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3bi) Orange solid (364.65 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 11.02 (s, 1H), 10.78 (s, 1H), 10.11 (s, br, 2H), 8.44 (s, 1H), 8.11 – 8.07 (m, 2H), 5.54 (d, *J*= 2.0 Hz, 1H), 4.46 (d, *J*= 2.0 Hz, 1H), 3.98 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 181.6, 178.2, 160.1, 159.1, 153.9, 144.1, 143.7, 127.0, 121.2, 119.1, 117.13, 101.5, 59.4, 54.9, 41.8. **HRMS (+ESI)** calcd. for $C_{16}H_{12}N_4O_6S$ $(M+H)^+$: 388.0478 found*:* 388.0475

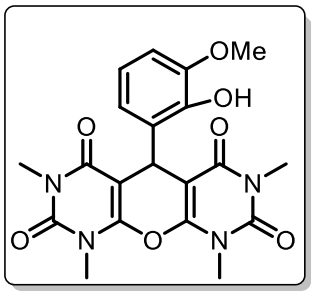


5-(7-bromo-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (3bj) Deep yellow solid (382.71 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 10.98 (s, 1H), 10.69 (s, 1H), 9.87 (s, br, 2H), 8.51 (s, 1H), 8.13 – 8.09 (m, 2H), 5.16 (d, *J*= 2.5 Hz, 1H), 4.17 (d, *J*= 2.5 Hz, 1H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 179.6, 178.2, 159.1, 153.9, 150.8, 144.7, 136.8, 135.0, 128.4, 123.7, 102.5, 57.7, 42.4. **HRMS (+ESI)** calcd. for $C_{15}H_9BrN_4O_5S$ $(M+H)^+$: 435.9477 found*:*

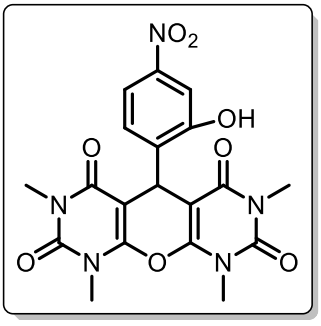
435.9486



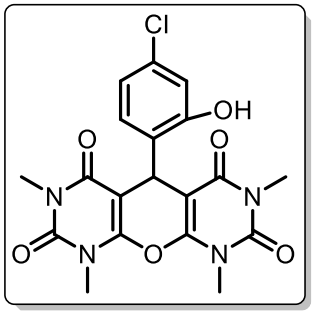
5-(2-hydroxyphenyl)-1,3,7,9-tetramethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4a) Pale yellow solid (382.17 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 7.40-7.33 (m, 4H), 6.21 (s, br, 1H), 4.11 (s, 1H), 3.25 (s, 6H), 3.08 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 164.2, 157.8, 153.9, 146.8, 132.3, 131.9, 131.6, 121.0, 118.2, 104.2, 48.7, 34.5, 32.7. **HRMS (+ESI)** calcd. for $C_{19}H_{18}N_4O_6$ $(M+H)^+$: 398.1226 found*:* 398.1242



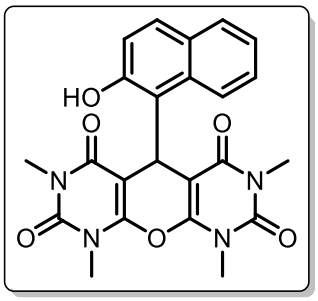
5-(2-hydroxy-3-methoxyphenyl)-1,3,7,9-tetramethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4b) pale yellow solid (402.51 mg) **^{1}H NMR** (400 MHz, DMSO-$_6$) δ 7.16 (d, *J*= 8.2 Hz, 1H), 6.91-6.96 (m, 1H), 6.56 (d, *J*= Hz, 1H), 5.84 (s, br, 1H), 4.38 (s, 1H), 3.41 (s, 3H), 3.14 (s, 6H), 2.92 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 164.1, 157.9, 150.1, 148.8, 146.5, 134.4, 125.6, 120.8, 118.8, 104.2, 58.7, 49.3, 33.5, 29.8. **HRMS (+ESI)** calcd. for $C_{20}H_{20}N_4O_7$ $(M+H)^+$: 428.1332 found*:* 428.1337



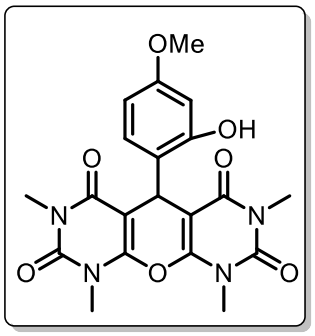
5-(2-hydroxy-4-nitrophenyl)-1,3,7,9-tetramethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4c) Yellow solid (372.19 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 7.75 (s, 1H), 7.66 (s, 1H), 7.55 (s, 1H), 4.40 (s, 1H), 3.98 (s, 1H), 3.14 – 3.10 (m, 6H), 2.92 – 2.88 (m, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 162.4, 155.8, 151.4, 149.2, 144.5, 134.8, 129.3, 115.9, 109.2, 102.2, 45.7, 30.9, 28.7. **HRMS (+ESI)** calcd. for $C_{19}H_{17}N_5O_8$ $(M+H)^+$: 443.1077 found*:* 443.1083



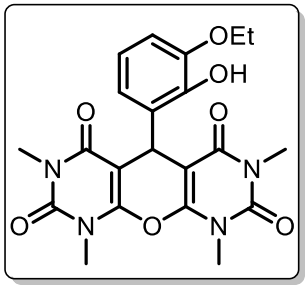
5-(4-chloro-2-hydroxyphenyl)-1,3,7,9-tetramethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4d) Off-white solid (388.86 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 7.14 (s, 1H), 6.87-6.72 (m, 2H), 5.49 (s, br, 1H), 4.56 (s, 1H), 3.21 (s, 6H), 3.05 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 165.2, 160.9, 157.4, 149.1, 138.5, 136.3, 134.0, 125.1, 121.2, 107.6, 49.7, 35.5, 33.8. **HRMS (+ESI)** calcd. for $C_{19}H_{17}ClN_4O_6$ $(M+H)^+$: 432.0837 found*:* 432.0851



5-(2-hydroxynaphthalen-1-yl)-1,3,7,9-tetramethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4e) Deep yellow solid (376.48 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 7.67-7.58 (m, 6H), 5.32 (s, br, 1H), 4.99 (s, 1H), 3.36 (s, 6H), 3.11 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 163.4, 156.9, 155.5, 144.2, 133.1, 130.3, 129.4, 127.5, 127.2, 120.5, 119.8, 102.3, 52.2, 33.9, 30.7. **HRMS (+ESI)** calcd. for $C_{23}H_{20}N_4O_6$ $(M+H)^+$: 448.1383 found*:* 448.1396



5-(2-hydroxy-4-methoxyphenyl)-1,3,7,9-tetramethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4f) Pale yellow solid (389.63 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 7.76 (s, 1H), 7.39 (d, 7.8 Hz, 1H), 6.87 (d, J = 7.4 Hz, 1H), 5.55 (s, br, 1H), 4.36 (s, 1H), 3.75-3.80 (m, 3H), 3.21 (s, 6H), 3.02 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 165.4, 163.9, 158.8, 157.4, 147.5, 134.1, 125.2, 108.3, 105.6, 104.7, 59.0, 49.7, 33.9, 31.7. **HRMS (+ESI)** calcd. for $C_{20}H_{20}N_4O_7$ $(M+H)^+$: 428.1332 found*:* 428.1347



5-(3-ethoxy-2-hydroxyphenyl)-1,3,7,9-tetramethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4g) Pale yellow solid (406.86 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 7.26 (d, *J*= 8.2 Hz, 1H), 7.04 (d, *J*= 8.2 Hz, 1H), 6.69 (t, *J*=7.8 Hz, 1H), 5.46 (s, br, 1H), 4.87 (s, 1H), 4.09 – 3.97 (m, 2H), 3.45 (s, 6H), 3.12 (s, 6H), 1.71 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 166.2, 159.8, 151.4, 150.1, 148.8, 133.9, 127.1, 123.9, 123.3, 106.6, 68.2, 50.8, 35.9, 32.7, 17.3. **HRMS (+ESI)** calcd. for $C_{21}H_{22}N_4O_7$ $(M+H)^+$: 442.1488 found*:* 442.1496

3.1.6 REPRESENTATIVE NMR SPECTRA

Figure 3.1.2 ^{1}H NMR Spectrum of 3aa in Chloroform-D

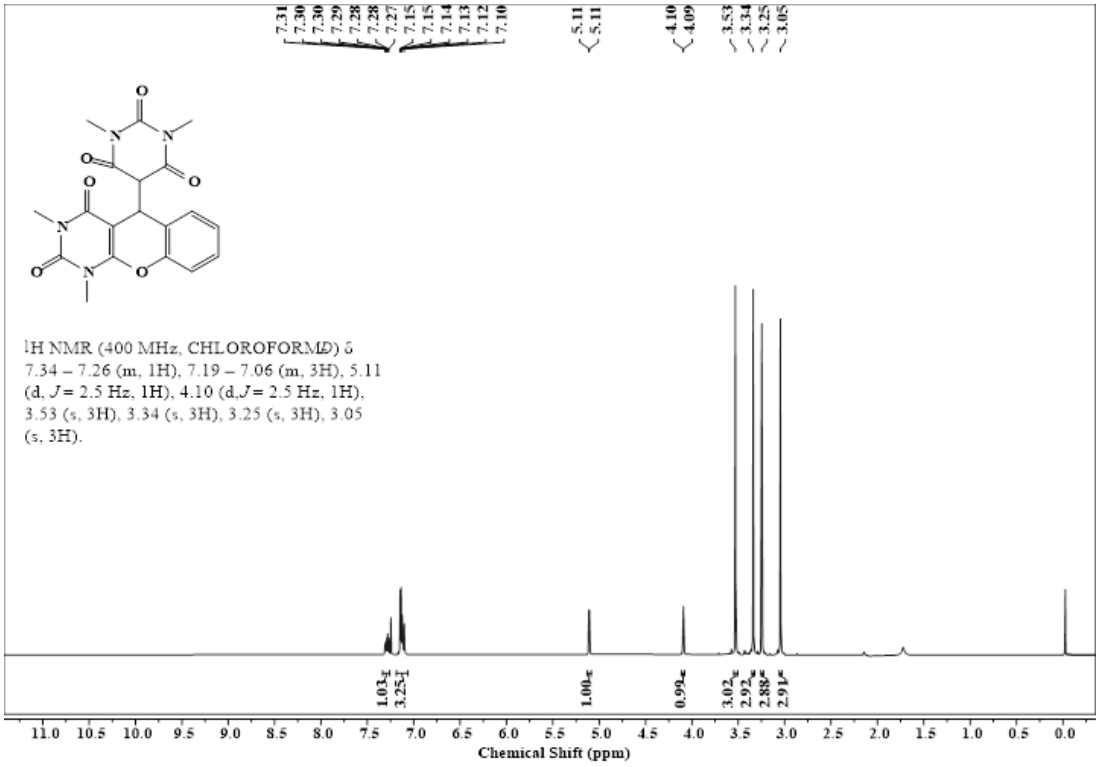
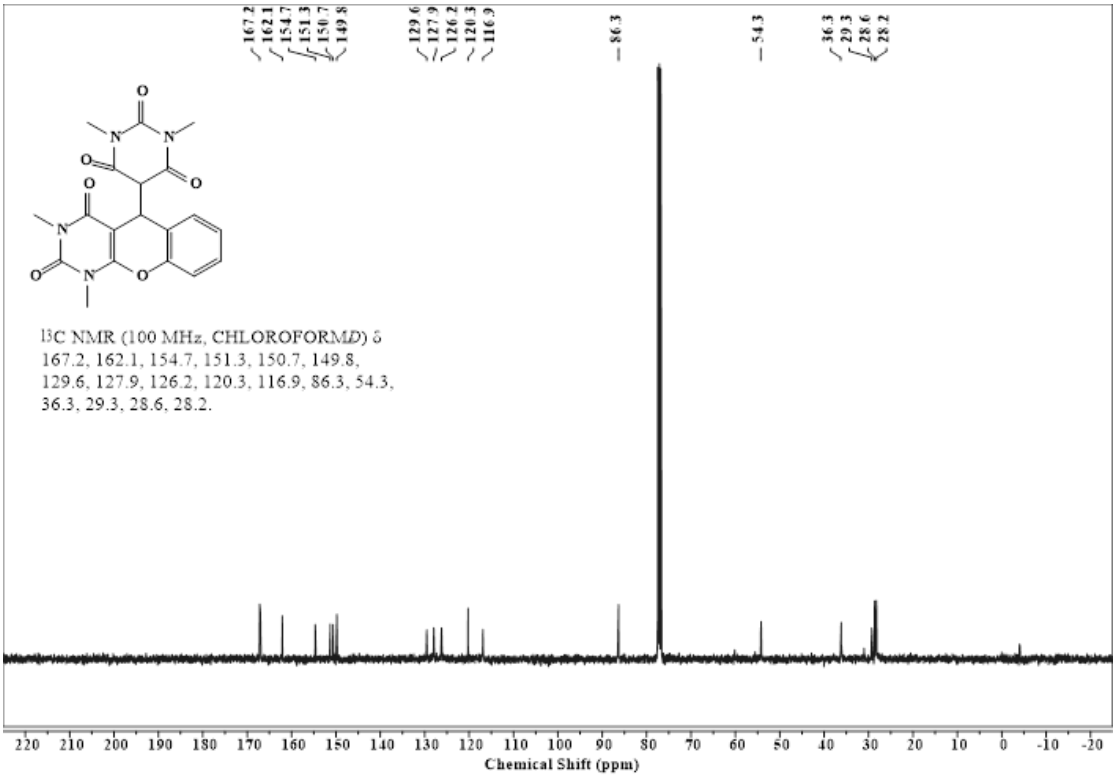
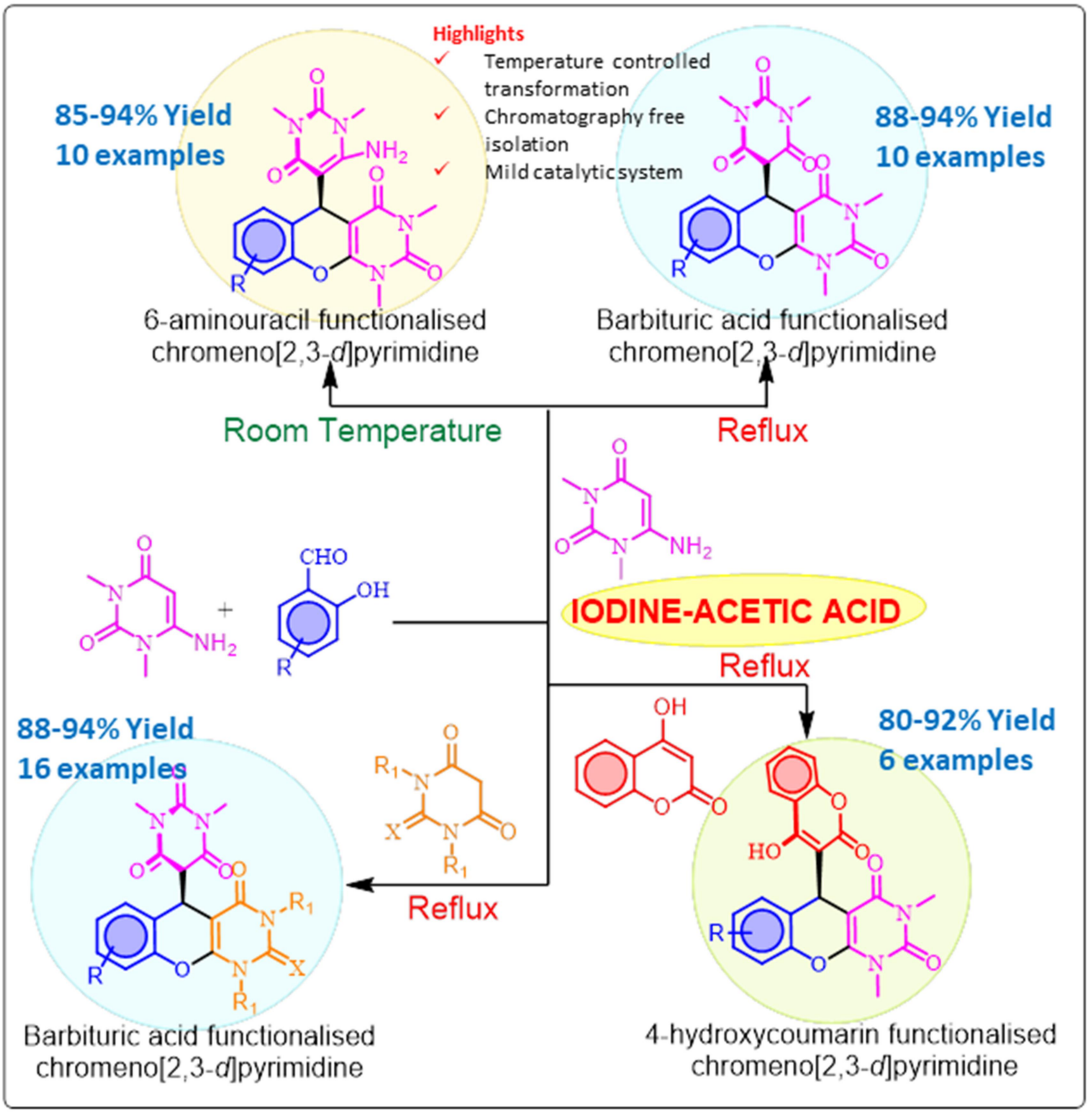


Figure 3.1.3 ^{13}C NMR Spectrum of 3aa in Chloroform-D



Section 3.2

Iodine-acetic acid catalysed synthesis of 6-aminouracil, 4-hydroxycoumarin, and barbituric acid functionalised chromeno[2,3-*d*]pyrimidines

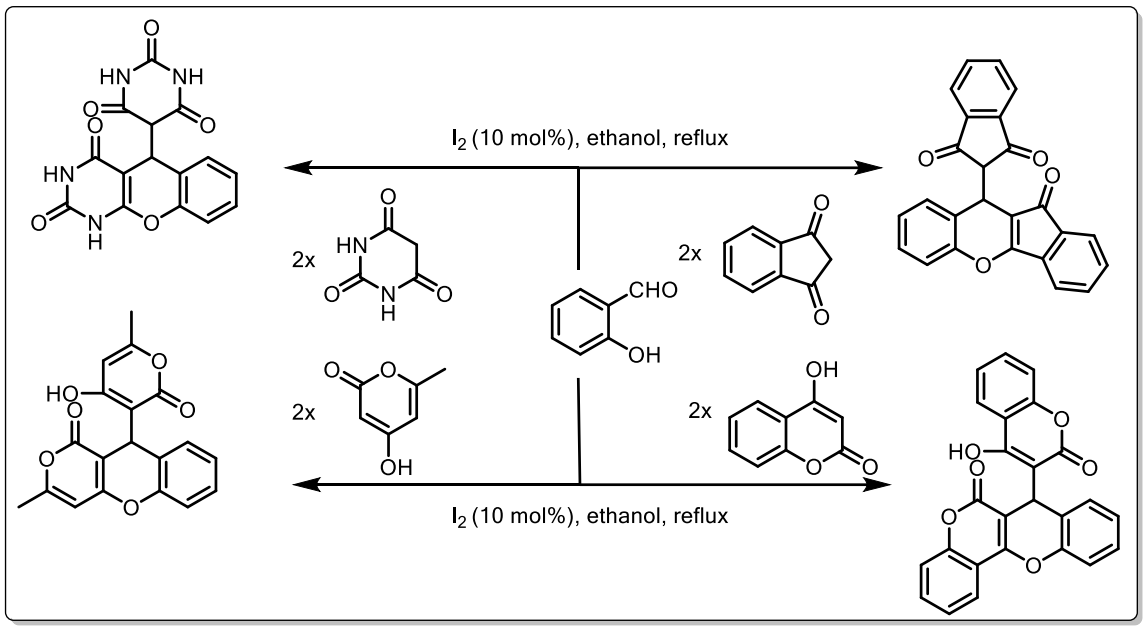


3.2.1 INTRODUCTION

It is a well-known fact that pyrimidine-embedded heterocyclic molecules constitute an important segment of natural and synthetic products, of which quite a good number have pronounced biological activity and many have found applications in pharmaceutics [51, 52]. In the introductory segment of this chapter, chromenopyrimidines have been discussed in details. In continuation of our interests in creating this class of fused heterocycles and in the concept of molecular hybridization, we have explored the possible ways of synthesizing heterocycles functionalized chromenopyrimidines. In the previous section (**section 3.1**), the base directed synthesis of barbiturate functionalized chromeno[2,3-*d*]pyrimidines was discussed. The method, although green, suffered from the fact that the amount of base required was stoichiometric. The process bore the prospect of getting greener if the amount of the mediator could be reduced to the catalytic scale. But, it was also revealed that if the amount of base was reduced then the reaction was affected by lowering of the yield. Therefore, it was necessary to derive another protocol, so that the synthesis of heterocycle functionalized chromeno[2,3-*d*]pyrimidines could be approached from another dimension and made greener with equal, if not more, efficacy. While searching for earlier reports on the synthesis of the mentioned class of hybrid fused heterocyclic compounds, some important information came to the front.

Zang *et al.* in 2012 reported an iodine catalyzed synthesis of chromene derivatives, where 2-hydroxybenzaldehyde was shown to participate in a double condensation reaction with two equivalents of indanone, barbituric acids, 4-

hydroxycoumarins or 4-hydroxy-6-methylpyran-2-one (**scheme 3.2.1**). This was one of the first reports of its kind where heterocycles functionalized chromene derivatives were synthesized [53].

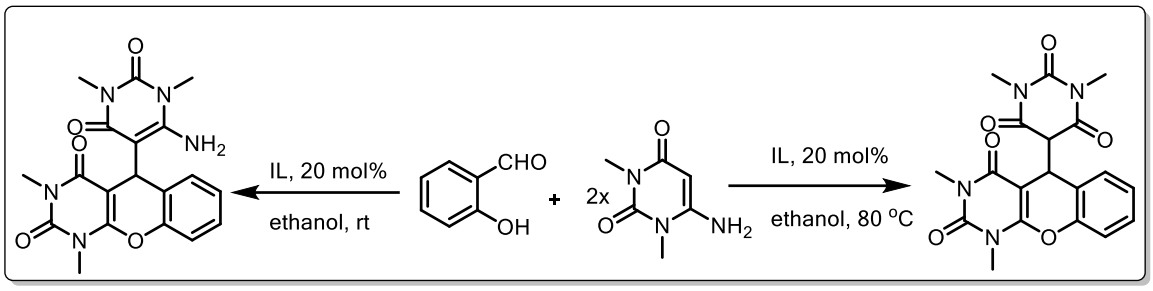


Scheme 3.2.1 Molecular iodine catalysed synthesis of heterocycle functionalised chromene derivatives (Zang *et al.*)

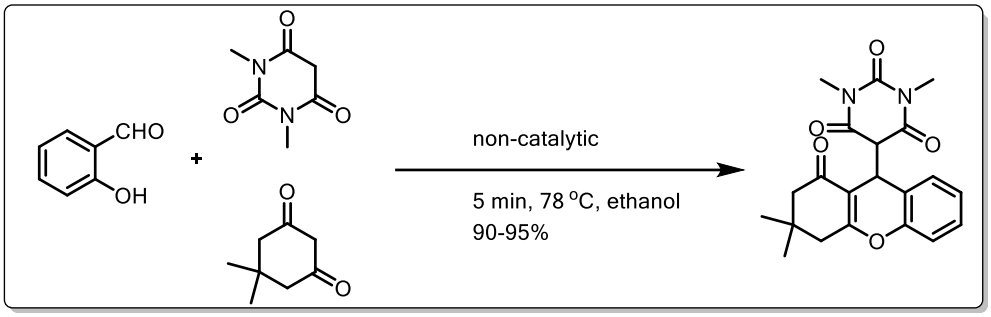
Patil *et al.* in 2014 showed a similar transformation using 1,1'-sulfinyldipyridinium *bis*(hydrogen sulphate) ionic liquid. They reported the formation of two different kinds of heterocycles fused chromene derivatives by altering the reaction conditions. While, 6-aminouracil functionalized chromeno[2,3-*d*]pyrimidines were formed at room temperature; elevated temperature resulted in the functional group transformation of 6-aminouracil to barbiturate and therefore, resulted in the formation of barbiturate functionalized chromeno[2,3-*d*]pyrimidines (**scheme 3.2.2**) [54].

Elinson *et al.* in 2015 reported a non-catalytic MCR of salicylaldehydes, dimedone and barbituric acid towards the formation of substituted tetrahydro-1*H*-

xanthen-1-ones (**scheme 3.2.3**). The preferential cyclisation through the carbonyl carbon of a ketone in the presence of another amidic carbonyl group was the highlight of the reaction [55].

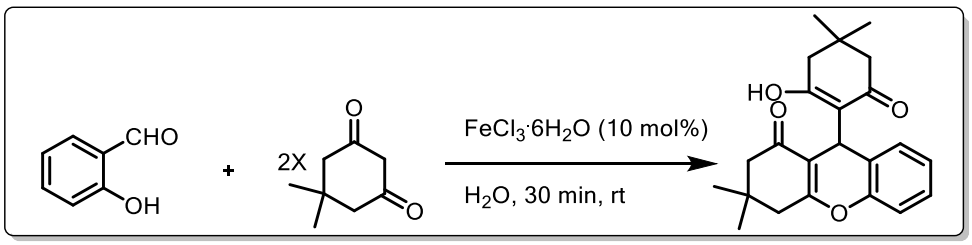


Scheme 3.2.2 Ionic liquid catalysed and temperature controlled synthesis of 6-aminouracil and barbiturate functionalised chromeno[2,3-*d*]pyrimidines (Patil *et al.*)



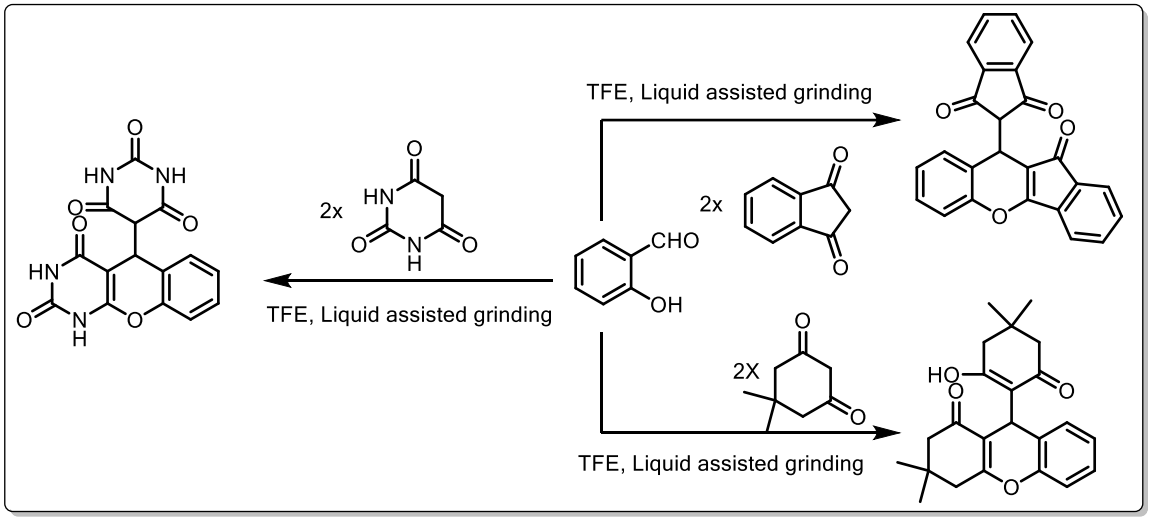
Scheme 3.2.3 Non-catalytic MCR for the synthesis of substituted tetrahydro-1*H*-xanthen-1-ones (Elinson *et al.*)

Tajbakhsh *et al.* in 2016 reported $FeCl_3{\cdot}6H_2O$ catalysed synthesis of xanthenes by the condensation of salicylaldehyde with 1,3-diketones in aqueous media (**scheme 3.2.4**) [56].



Scheme 3.2.4 $FeCl_3{\cdot}6H_2O$ catalysed synthesis of xanthenes (Tajbakhsh *et al.*)

Lohar *et al.* in 2018 reported 1,1,2,2-tetrafluoroethane (TFE) catalyzed liquid assisted grinding method for the synthesis of chromene and isoindolo[2,1-*a*]quinazoline scaffolds (**scheme 3.2.5**). The chemistry behind the reaction was quite similar to the report by Zang *et al.* and it comprised of condensing 2-hydroxybenzaldehydes with two equivalents of active methylene compounds like indanone, dimedone and barbituric acid [57].

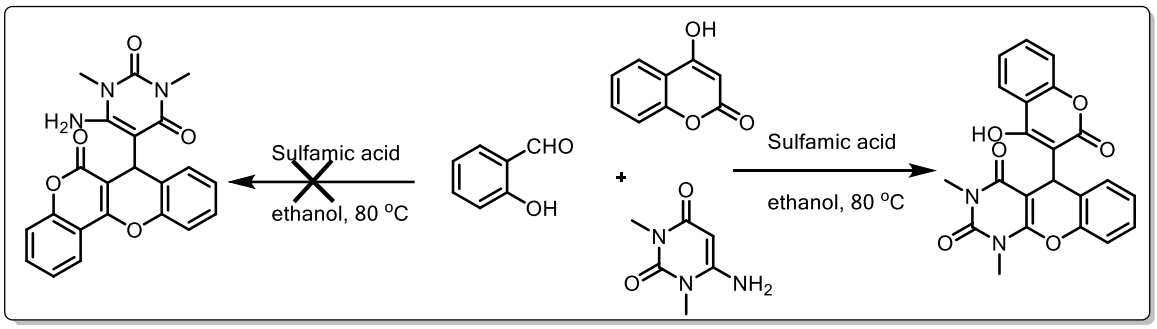


Scheme 3.2.5 TFE catalyzed liquid assisted grinding method for the synthesis of chromene and isoindolo[2,1-*a*]quinazoline scaffolds (Lohar *et al.*)

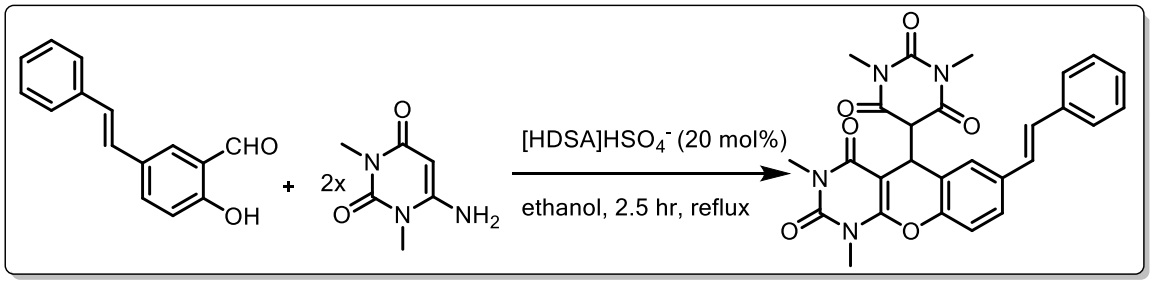
Dige *et al.* in 2019 reported a sulfamic acid catalyzed synthesis of 4-hydroxy-coumarin functionalized chromeno[2,3-*d*]pyrimidines *via* MCR between 2-hydroxybenzaldehydes, 4-hydroxy-coumarin and 6-aminouracils (**scheme 3.2.6**). The usage of acid catalyst directed the reaction towards preferential deaminative cyclisation, instead of the dehydrogenative path. This, in turn, resulted in the exclusive formation of the chromenopyrimidine ring over benzochromenes [58].

Korade *et al.* in 2020 reported an ionic liquid ([HDSA]HSO_4^-) catalyzed synthesis of aryldiazo substituted heterocycles, where the heterocyclic part comprised of

barbiturate functionalized chromeno[2,3-*d*]pyrimidines (**scheme 3.2.7**). It was formed by condensing a diazo group containing 2-hydroxybenzaldehyde with two equivalents of barbituric acid or dimedone [59].



Scheme 3.2.6 Sulfamic acid catalyzed synthesis of 4-hydroxy-coumarin functionalized chromeno[2,3-*d*]pyrimidines (Dige *et al.*)



Scheme 3.2.7 [HDSA]HSO_4^- catalysed synthesis of aryldiazo substituted heterocycles (Korade *et al.*)

The essential takeaways from these reports were:

a. The formation of heterocycle functionalized chromeno[2,3-*d*]pyrimidines could be carried out in the presence of acid catalyst

b. The products being solid would be difficult to isolate from a mixture containing heterogeneous catalyst. Therefore, homogeneous catalytic system is preferred/ required.

c. 6-aminouracils transform into barbiturates when refluxed under acidic conditions.

d. Regioselectivity of the formation of the chromeno ring is dependent upon the reactivity of the groups coming together for condensation. It can be deaminative or dehydrogenative depending upon the lability of the leaving group and stability of the corresponding compound formed.

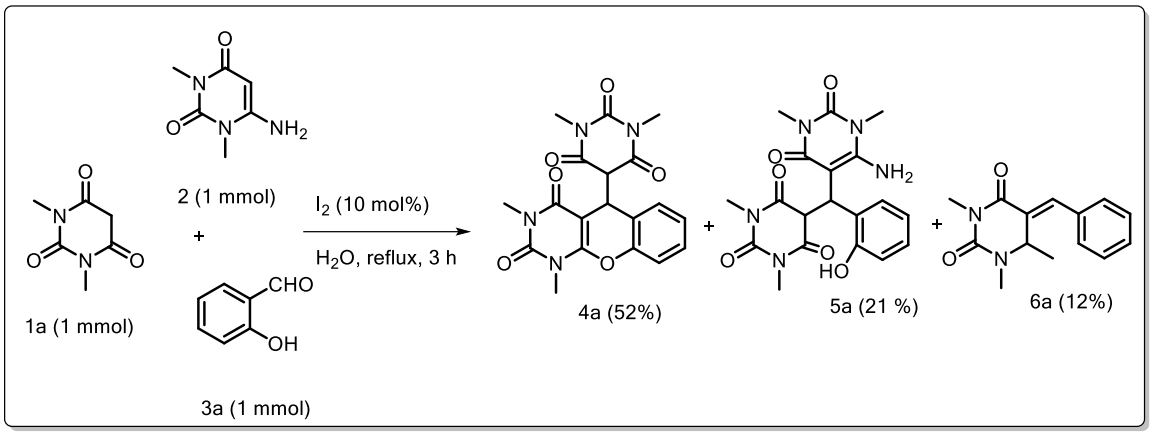
It is a common practice to use ionic liquids in organic synthesis by terming it as a greener alternative. However, its preparation requires another effort, thereby questioning the step-economy of the overall reaction protocol. There are a number of Lewis acid catalysts which would work just efficiently as ionic liquids and the activity of one such catalyst, $FeCl_3 \cdot 6H_2O$, has already been seen in **section 2.2**. Another remarkable Lewis acid that has gained popularity in domains of organic synthesis, especially with MCRs, is molecular iodine [60].

Previously, (in **section 3.1**), the base mediated synthesis of barbiturate functionalized chromeno[2,3-*d*]pyrimidines was reported. One of the shortcomings of the method was the usage of stoichiometric amount of base. From the study of reported methods for the synthesis of chromeno[2,3-*d*]pyrimidines, acid catalysts could turn out to be better alternatives. Therefore, with an aim to synthesize heterocycle functionalized chromeno[2,3-*d*]pyrimidines by utilizing the aid of molecular iodine catalysis, a study was conducted with 2-hydroxybenzaldehydes, barbituric acids and 6-aminouracils.

3.2.2 RESULTS AND DISCUSSION

Building on the objective of designing a protocol for the synthesis of heterocycle functionalized chromeno[2,3-*d*]pyrimidines *via* molecular iodine catalysis, equimolar quantities of 2-hydroxybenzaldehyde, *N,N'*-dimethylbarbituric acid and

N,N'-dimethyl-6-aminouracil was stirred to form a slurry with 5 mL distilled water. To this 10 mol% of molecular iodine was added and the reaction mixture was put under reflux for one hour. At the end of the designated hour, the reaction was stopped and the reaction mixture was cooled. Upon cooling, The reaction mixture was analysed with the help of TLC and it was found that some amount of *N,N'*-dimethyl-6-aminouracil was left unreacted along with some amount of the benzylidene barbiturate formed *via* the Knoevenagel condensation between 2-hydroxybenzaldehyde and *N,N'*-dimethylbarbituric acid. There were two new spots on the TLC. One was expected to be the product formed after the nucleophilic addition of *N,N'*-dimethyl-6-aminouracil to the benzylidene barbiturate and the second one could be the condensed chromenopyrimidine product. To ensure that the reaction goes into completion upon increasing the reaction time, the reaction was restarted under reflux and continued for another two hours. After the end of a three hour period, the reaction was removed from refluxed and cooled. The reaction mixture was again analysed by TLC but no further progress in the reaction was observed. Consequently workup was followed and the reaction mixture was treated with water and DCM. The organic layer was collected and treated with anhydrous sodium sulphate. Upon concentration of the organic layer, it was subjected to column chromatography through silica gel 60-120 mesh and eluted with 20-50% ethylacetate-hexane mixture. The isolated products were subjected to concentration under reduced pressure and then further dried by storing under vacuum. They were then analysed *via* NMR spectroscopy and mass spectrometry. The results of the initial observations are summarized in **scheme 3.2.8**.



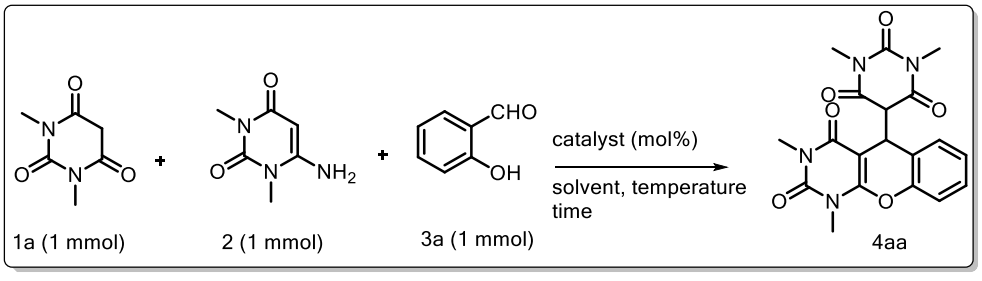
Scheme 3.2.8 Initial observations of the molecular iodine catalysed MCR between 2-hydroxybenzaldehyde, *N,N'*-dimethylbarbituric acid and *N,N'*-dimethyl-6-aminouracil

The formation of the barbiturate functionalised chromeno[2,3-*d*]pyrimidine was confirmed by the presence of the characteristic –CH tertiary methyl proton peaks of the chromene ring and the barbiturate group showing resonance as doublets at δ 5.11 ppm and 4.10 ppm respectively. In ^{13}C NMR, both the tertiary methyl –CH carbons showed resonance at δ 36.3 ppm and 54.3 ppm respectively. The mass spectrum showed a molecular ion peak at m/z $(M+H)^+$ 398.1229, which correlated with its molecular formula: $C_{19}H_{18}N_4O_6$.

Following these encouraging results, improving the yields of the reaction was the next objective. For this, the amount of the iodine catalyst was increased to 20 mol% but the yields remained the same. It must also be mentioned that the desired product was not formed in the absence of iodine catalyst. Also, other homogeneous Lewis acids such as $FeCl_3{\cdot}6H_2O$, $AlCl_3$, and $NiCl_2{\cdot}6H_2O$ (**entries 9-11 of table 3.2.**1) and some protic acids such as sulfuric acid, sulfamic acid, acetic acid and orthophosphoric acid (**entries 12-15 of table 3.2.1**) were also tested. While the Lewis acids produced results similar to iodine, the protic acids showed some improvement to the results. However, the usage of strong acids

such as sulfuric acid is discouraged due to handling issues. The reaction was also carried out with iodine as catalyst in different solvents such as ethanol, DMF and DMSO (**entries 5-8 of table 3.2.1**), but the best results were still obtained with water (**entry 1 of table 3.2.1**). As the study on the effect of different acids on the reaction yields revealed that better results could be obtained with the help of protic acid, a study was conducted by using acetic acid and orthophosphoric acid (milder protic acids) as additives (**entries 16-18 of table 3.2.1**) along with the iodine catalyst. It was revealed that the activity of the catalytic system improved by manifolds when additives (especially acetic acid), were used along with molecular iodine. Therefore, the subsequent studies were conducted by using molecular iodine-acetic acid combination for the catalytic system. It was observed that 10 mol% each of iodine catalyst and acetic acid additive was optimum (94% isolated yield) (**entry 19 of table 3.2.1**). The reaction required elevated temperature (reflux) for completion and the maximum time required for the reaction to complete was 30 minutes. The results of the optimisation of reaction conditions are summarised in **table 3.2.1**

Table 3.2.1 Optimisation of the reaction

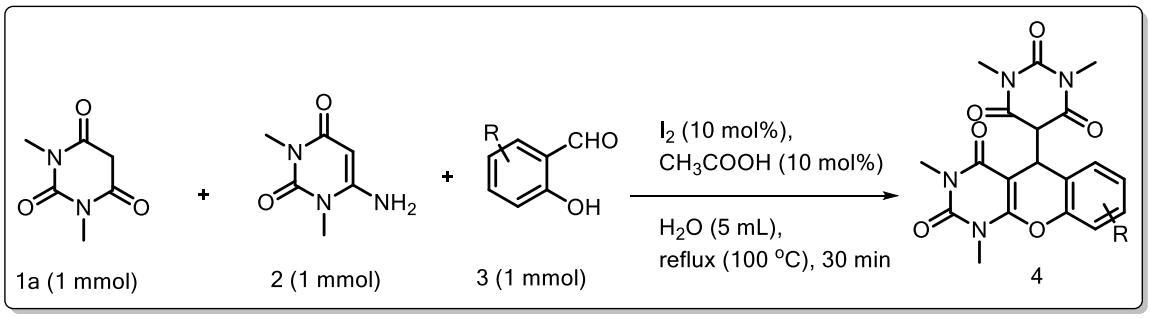


Entry	Catalyst (mol%)	Additive (mol%)	Solvent (5 mL)	Time (min)	Temperature (°C)	Isolated Yield %
1	**Iodine (I_2) (10)**	-	H_2O	60	reflux	52
2	**Iodine (I_2) (20)**	-	H_2O	60	reflux	52

3	**Iodine (I_2) (5)**	-	H_2O	60	reflux	36
4	**No catalyst**	-	H_2O	60	reflux	nr [b]
5	Iodine (I_2) (10)	-	**EtOH**	30	reflux	39
6	Iodine (I_2) (10)	-	**DMF**	30	reflux	Traces
7	Iodine (I_2) (10)	-	**DMSO**	30	reflux	26
8	Iodine (I_2) (10)	-	**Toluene**	30	reflux	nr[c]
9	**$FeCl_3 \cdot 6H_2O$ (10)**	-	H_2O	60	reflux	50
10	**$AlCl_3$ (10)**	-	H_2O	60	reflux	46
11	**$NiCl_2 \cdot 6H_2O$ (10)**	-	H_2O	60	reflux	28
12	**H_2SO_4 (10)**	-	H_2O	60	reflux	79
13	**Sulfamic acid (10)**	-	H_2O	60	reflux	76
14	**CH_3COOH (10)**	-	H_2O	60	reflux	72
15	**H_3PO_4 (10)**	-	H_2O	60	reflux	58
16	Iodine (I_2) (10)	**H_3PO_4 (10)**	H_2O	60	reflux	69
17	Iodine (I_2) (10)	**CH_3COOH (10)**	H_2O	60	reflux	94
18	Iodine (I_2) (10)	**CH_3COOH (20)**	H_2O	60	reflux	94
19[a]	**Iodine (I_2) (10)**	**CH_3COOH (10)**	**H_2O**	**30**	**reflux**	**94**
20	Iodine (I_2) (10)	CH_3COOH (10)	H_2O	**15**	**reflux**	85
21	Iodine (I_2) (10)	CH_3COOH (10)	H_2O	30	**rt**	nr[b]
22	Iodine (I_2) (10)	CH_3COOH (10)	H_2O	30	**70**	82

Reaction conditions: 2-hydroxybenzaldehyde (1 mmol, 0.122 g), *N,N'*-dimethylbarbituric acid (1 mmol, 0.156 g) and *N,N'*-dimethyl-6-aminouracil (1 mmol, 0.155 g), catalyst, additive, solvent, temperature, time. [a]Best reaction conditions. nr[b] reaction did not proceed beyond 5a. nr[c] no reaction was observed.

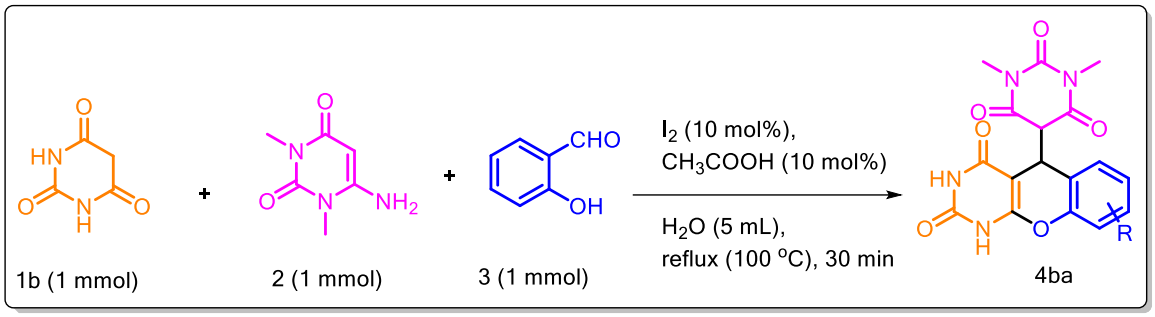
The optimized reaction conditions thus established led to the development of the reaction protocol (**scheme 3.2.9**).



Scheme 3.2.9 Optimised reaction scheme

It was easy to assume that the chromene ring was formed *via* deaminative cyclisation. But, a very crucial fact came into view when *N,N'*-dimethylbarbituric

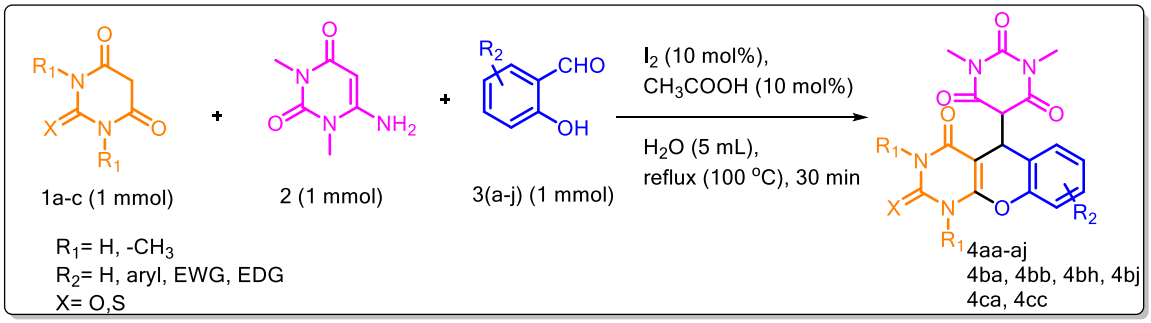
acid was replaced with barbituric acid. It was found that the chromene ring was formed by the condensation between the carbonyl group of the barbituric acid and the hydroxyl group of the aromatic segment. Moreover, the amino group of *N,N'*-dimethyl-6-aminouracil, had undergone transformation into a carbonyl group. This was proven by the formation of the product **4ba** in **scheme 3.2.10**.

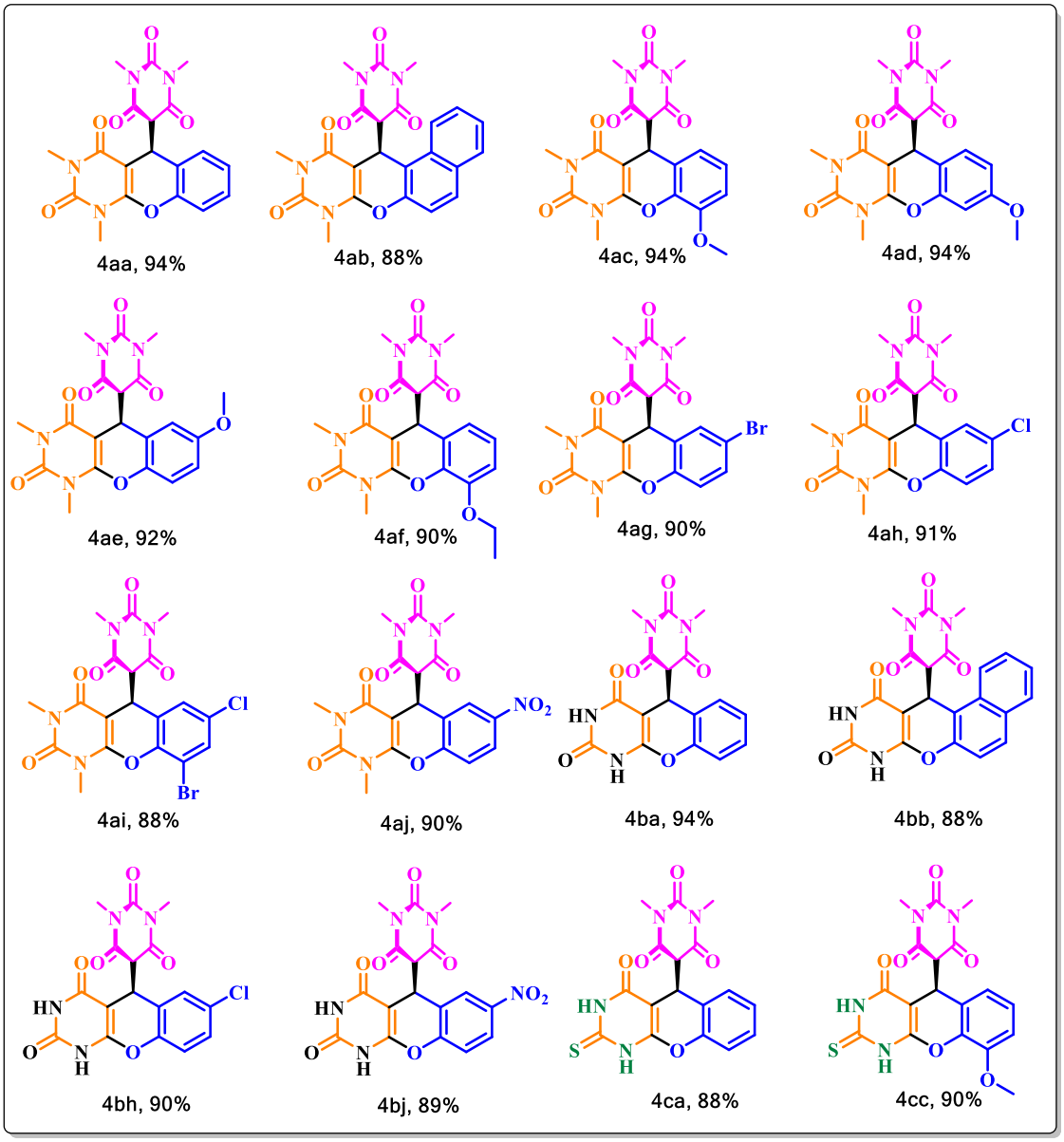


Scheme 3.2.10 Dehydrogenative cyclisation towards the formation of chromene ring and transformation of vinyl amine group to carbonyl group

Thus, after the nucleophillic addition of the 6-aminouracil group onto the benzylidene barbiturate substrate, the vinyl amine of 6-aminouracil undergoes functional group transformation into a carbonyl group in the presence of the acid catalyst and water. This is similar to the transformation carried out by $FeCl_3{\cdot}6H_2O$ in **section 2.2** of **chapter 2**. Following the establishment of the reaction protocol, the study was extended towards different substituted 2-hydroxybenzaldehydes and barbituric acids (**Scheme 3.2.11)**. It was observed that the reaction protocol was applicable to a wide range of substrates. The effect of the presence of electron donating and electron withdrawing groups was not pronounced. However, the presence of steric crowd led to decrease of yield. Additionally, all the products were solid and could be isolated by simple filtration. In short, chromatography free isolation of products was feasible.

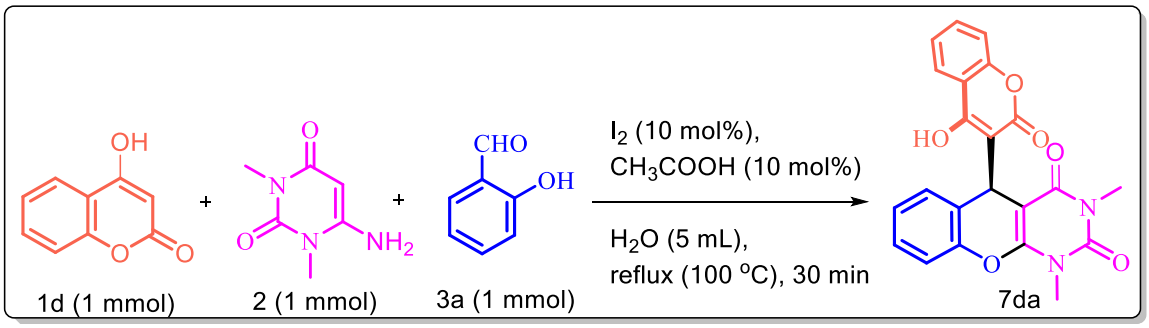
Scheme 3.2.11 Substrate study for I_2-acetic acid catalysed synthesis of barbiturate functionalised chromeno[2,3-*d*]pyrimidines





Reaction conditions: 2-hydroxybenzaldehydes (1 mmol), barbituric acids (1 mmol) and *N,N'*-dimethyl-6-aminouracil (1 mmol), I_2 (10 mol%), acetic acid (10 mol%), H_2O (5 mL), reflux , 30 min

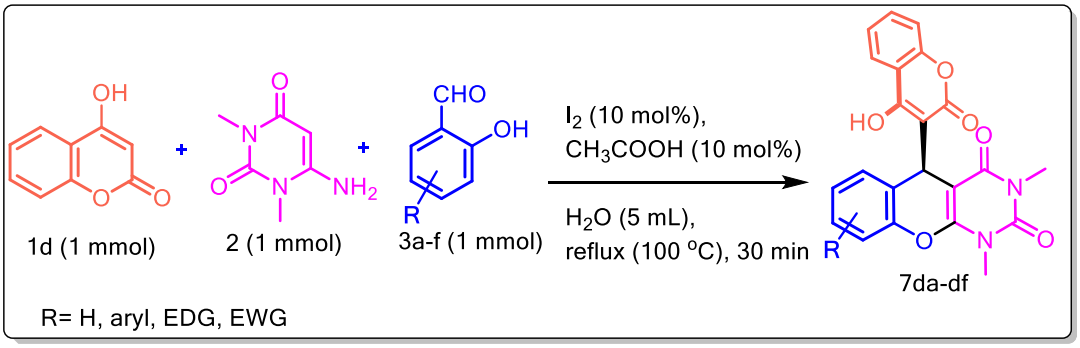
As it was revealed in the study that the pyrimidine segment of the chromenopyrimidine part comes from the barbituric acid, so, to check whether this was applicable to other heterocyclic moieties too, barbituric acid was replaced with 4-hydroxycoumarin and a reaction was carried out by following the same optimized conditions. However, when the product (**7a**) was analysed, it was found that 4-hydroxycoumarin did not participate in the chromene ring formation; rather, it became the substituent on it. It was the 6-aminouracil moiety, which now participated in the ring formation (**scheme 3.2.12**). Therefore, it can be said that the carbonyl group of the barbiturates possess high feasibility towards dehydrogenative ring formation under the given conditions.

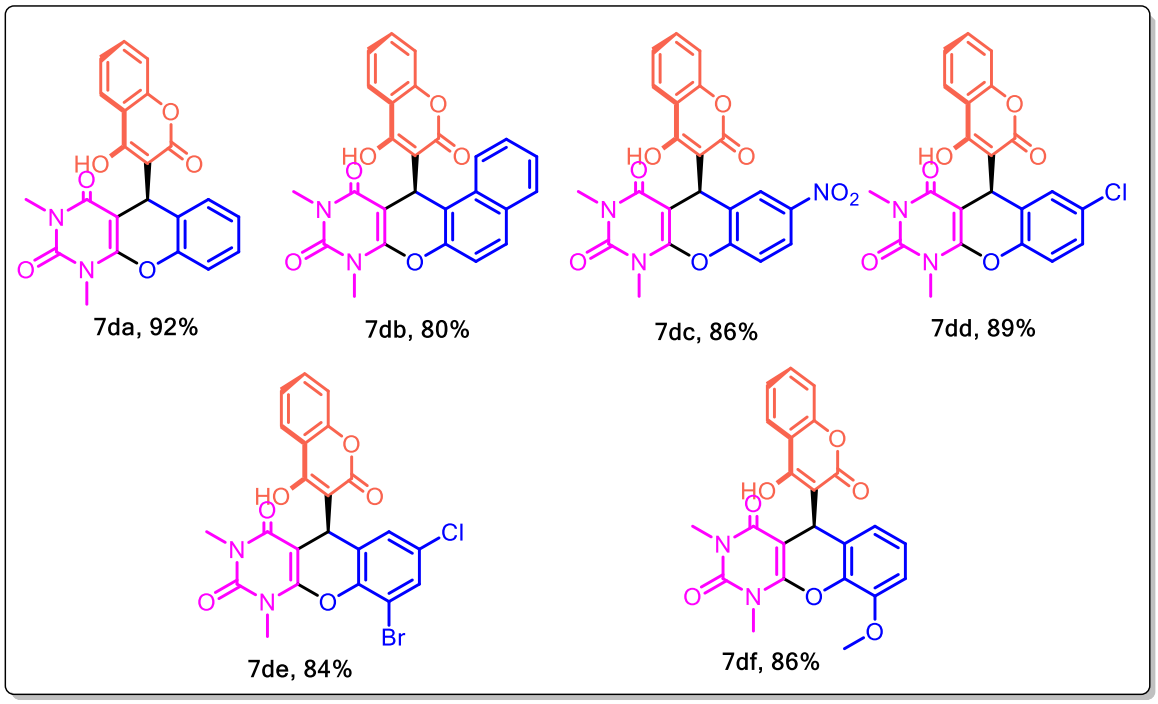


Scheme 3.2.12 Preferentiality towards the formation of chromene ring with pyrimidine segment over 4-hydroxycoumarin segment

The study was furthered by applying the protocol to different types of 2-hydroxybenzaldehydes and it was found that the products were formed in good to excellent yields (**scheme 3.2.13**). No significant effect from the electronic factors of the substituents was observed. However, steric factor controlled the conversion and thereby affected the yield of the products. The primary steric factor was included during the formation of the benzylidene moiety with 4-hydroxycoumarin. 4-hydroxycoumarin itself is a bulky group and the nucleophillic attack of 6-aminouracil on it was hindered to some extent.

Scheme 3.2.13 Substrate study for I_2-acetic acid catalysed synthesis of 4-hydroxycoumarin functionalised chromeno[2,3-*d*]pyrimidines





Reaction conditions: 2-hydroxybenzaldehydes (1 mmol), 4-hydroxycoumarin (1 mmol) and *N,N'*-dimethyl-6-aminouracil (1 mmol), I_2 (10 mol%), acetic acid (10 mol%), H_2O (5 mL), reflux , 30 min

The formation of the compound was confirmed with the help of NMR spectroscopy, mass spectrometry and single crystal X-Ray diffraction analysis. An ORTEP diagram of **7df,** with a 50% probability ellipsoid is shown in **figure 3.2.1**.

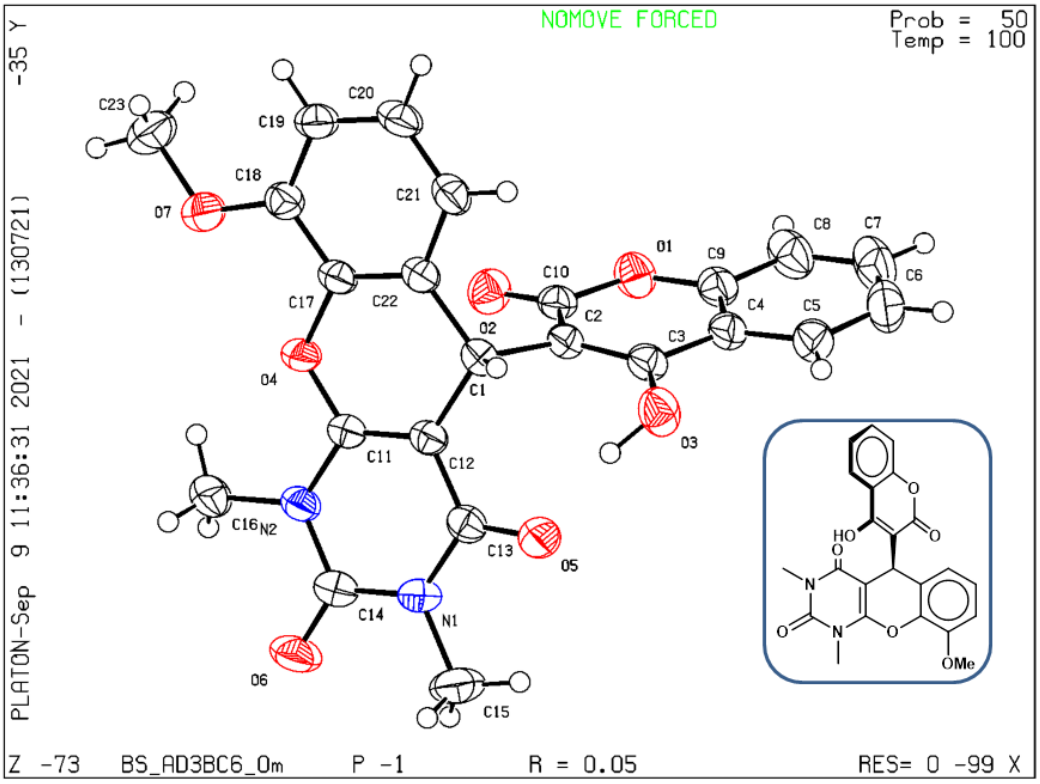
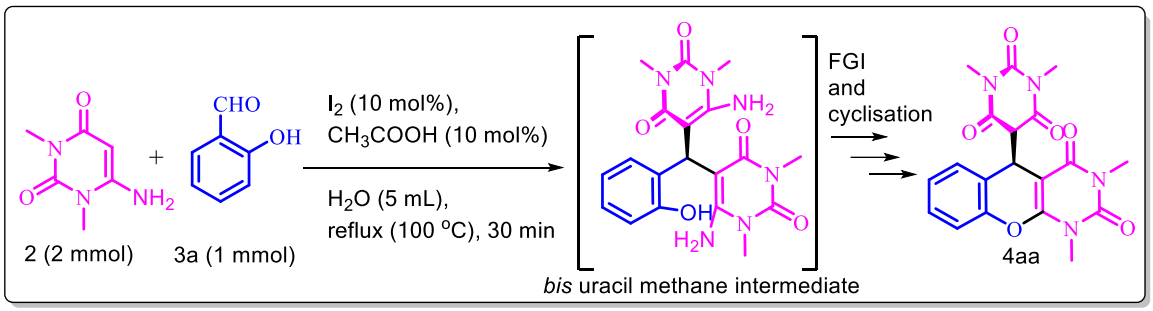


Figure 3.2.1 ORTEP diagram of **7df (CCDC depository number: 2124799)**

As discussed earlier that the vinyl amino group of 6-aminouracil undergoes an *in situ* transformation into a carbonyl group and converts into a barbiturate in the presence of Lewis acid and water under reflux conditions, therefore, a hypothesis arose to use two equivalents of 6-aminouracil along with 2-hydroxybenzaldehyde and synthesize barbiturate functionalized chromeno[2,3-*d*]pyrimidines. The concept behind this was to capitalize on the *in situ* transformation and carry forward with the reaction.

To begin the experimentation on this hypothesis, two equivalents of *N,N'*-dimethyl-6-aminouracil was treated with one equivalent of 2-hydroxybenzaldehyde under the same conditions and catalyst and refluxed for 30 minutes. The reaction was stopped at the end of the mentioned period and the

reaction mixture was analysed *via* TLC. To our surprise, the retention factor of the product formed matched with that of product **4aa**, meaning our hypothesis was proven correct (**scheme 3.2.14**). This was furthered with the study of the effect of substituents on 2-hydroxybenzaldehydes. It was observed that the reaction was as efficient as the earlier protocol (**scheme 3.2.11**) and the electronic factor of the substituents did not play a major role in determining the yield of the products. However, as previously observed, the steric factor did show its effects in the conversion (**scheme 3.2.15**). The reaction can be assumed to proceed through the formation of a *bis*-aminouracil methane intermediate (indicated by traces in the TLC study), followed by the transformation of the vinyl amino groups into carbonyls and then dehydrogenative cyclisation to result in the formation of the chromene ring.

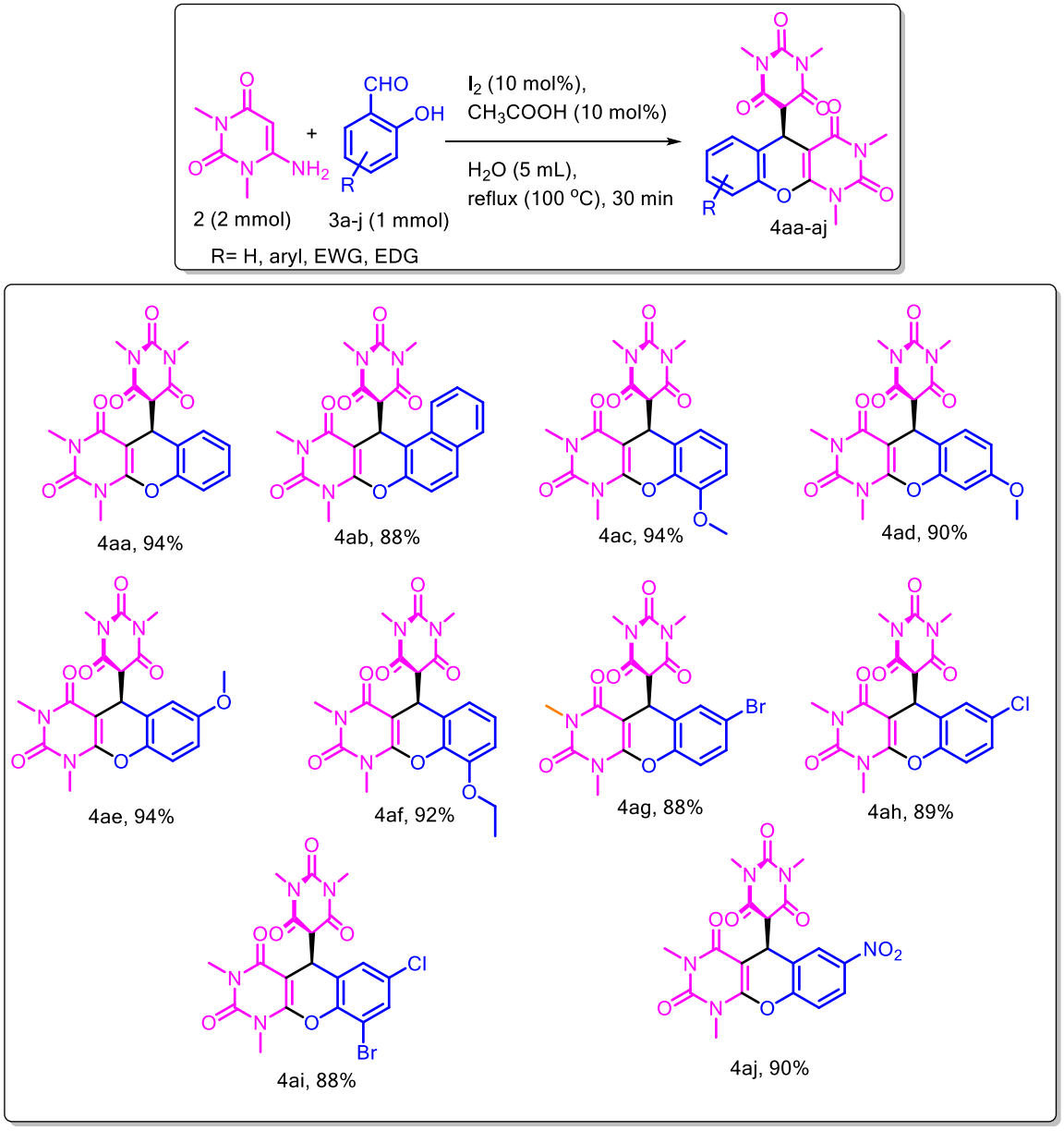


Scheme 3.2.14 Synthesis of barbiturate functionalised chromene[2,3-*d*]pyrimidine from 6-aminouracil and 2-hydroxybenzaldehyde

Since, the functional group transformation requires elevated temperature, therefore, to test the retention of the amine group and formation of 6-aminouracil functionalized chromene[2,3-*d*]pyrimidine the reaction was carried out at room temperature. It was expected that the reaction might go up to the *bis*-aminouracil methane stage and not proceed further. However, when the product was

analysed initially with the help of TLC, then the *bis*-aminouracil methane spot was absent.

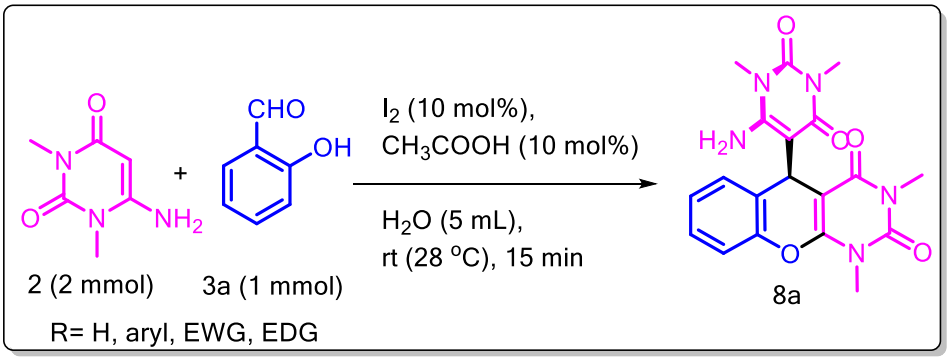
Scheme 3.2.15 Substrate study I_2-acetic acid catalysed synthesis of barbiturate functionalised chromeno[2,3-*d*]pyrimidines from 6-aminouracil and 2-hydroxybenzaldehyde



Reaction conditions: 2-hydroxybenzaldehydes (1 mmol), and *N,N'*-dimethyl-6-aminouracil (2 mmol), I_2 (10 mol%), acetic acid (10 mol%), H_2O (5 mL), reflux , 30 min

The solid product (**8a**) was isolated by filtration and washed with DCM, ethanol, and water. After drying under vacuum it was analysed with the help of NMR

spectroscopy and mass spectrometry. The presence of the characteristic tertiary methyl –CH proton in the ^{1}H NMR spectrum, showing resonance as a singlet at δ 5.35 ppm and the two –NH_2 protons showing resonance as a singlet at δ 6.04 ppm indicated the presence of only one vinyl amine group and the formation of 6-aminouracil functionalized chromeno[2,3-*d*]pyrimidine i.e, 5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione was ascertained. The ^{13}C NMR spectrum cleared the picture even more by indicating the formation of the chromene ring and the presence of four (and not three) different types of carbonyl carbons. The mass spectrum showed a molecular ion peak at m/z 397.3919 $(M+H)^+$, which correlated with its molecular formula: $C_{19}H_{19}N_5O_5$ (**scheme 3.2.16**). When the reaction was repeated and the time for the completion of the reaction was monitored, it was found that the reaction was complete within a span of 15 minutes.



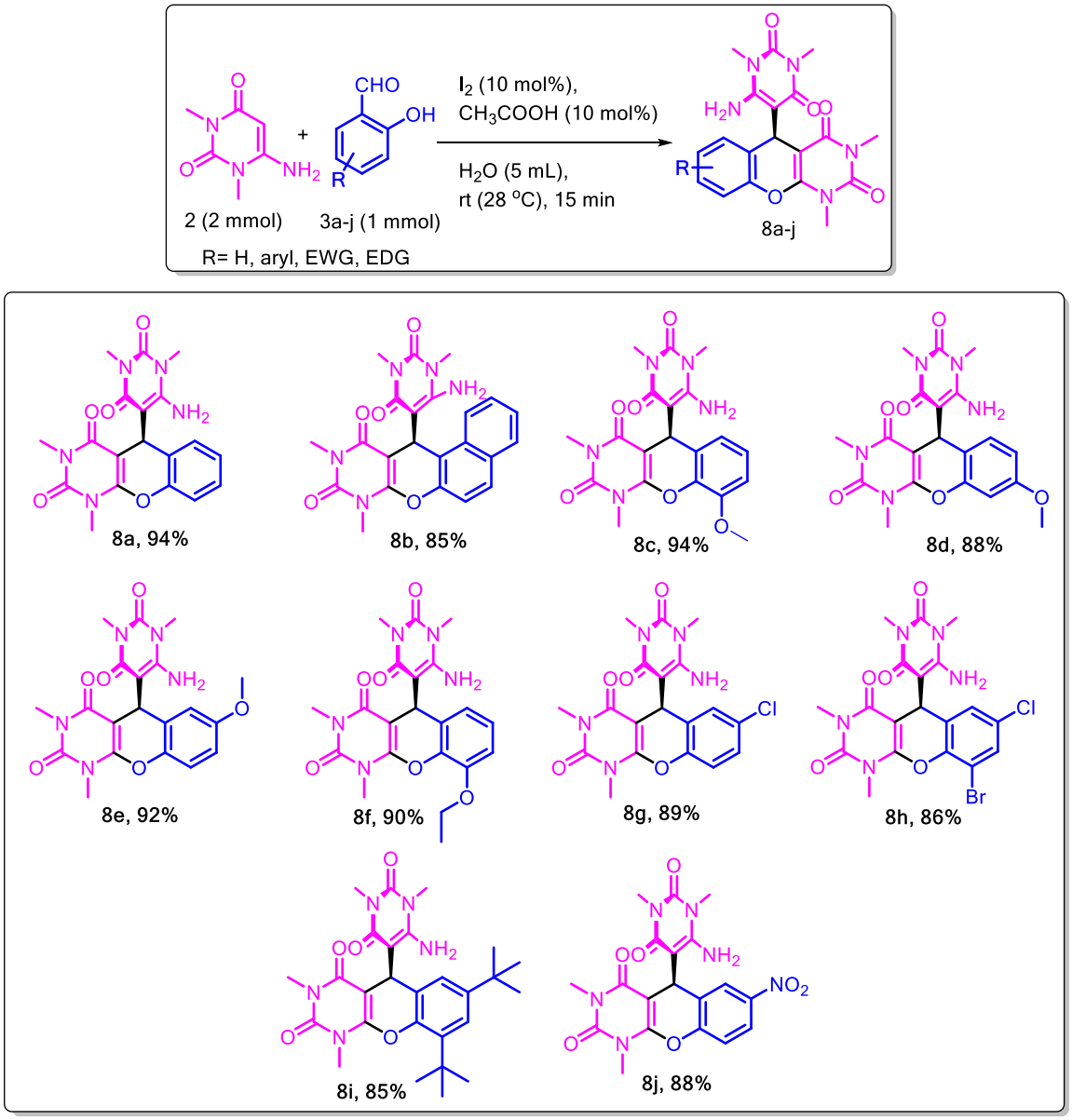
Scheme 3.2.16 Synthesis of 6-aminouracil functionalised chromeno[2,3-*d*]pyrimidines

The reaction was furthered towards studying the effect of substituents of 2-hydroxybenzaldehydes on the yield of the reaction; it was found that the electronic factors did not significantly affect the yields. However, the steric factor

affected the yields to some extent. The products formed were solid and were isolated by simple filtration and no further chromatographic methods were used.

The study of substrates is summarised in **scheme 3.2.17**.

Scheme 3.2.17 Substrate study I_2-acetic acid catalysed synthesis of 6-aminouracil functionalised chromeno[2,3-*d*]pyrimidines at room temperature



Reaction conditions: 2-hydroxybenzaldehydes (1 mmol), and *N,N'*-dimethyl-6-aminouracil (2 mmol), I_2 (10 mol%), acetic acid (10 mol%), H_2O (5 mL), rt (28 °C) , 15 min

The structure of the 6-aminouracil functionalised chromeno[2,3-*d*]pyrimidines can be further illustrated with the help of the single crystal X-Ray diffraction analysis of the molecule **8b**. The ORTEP diagram of **8b,** with a 50% probability ellipsoid is shown in **figure 3.2.2**.

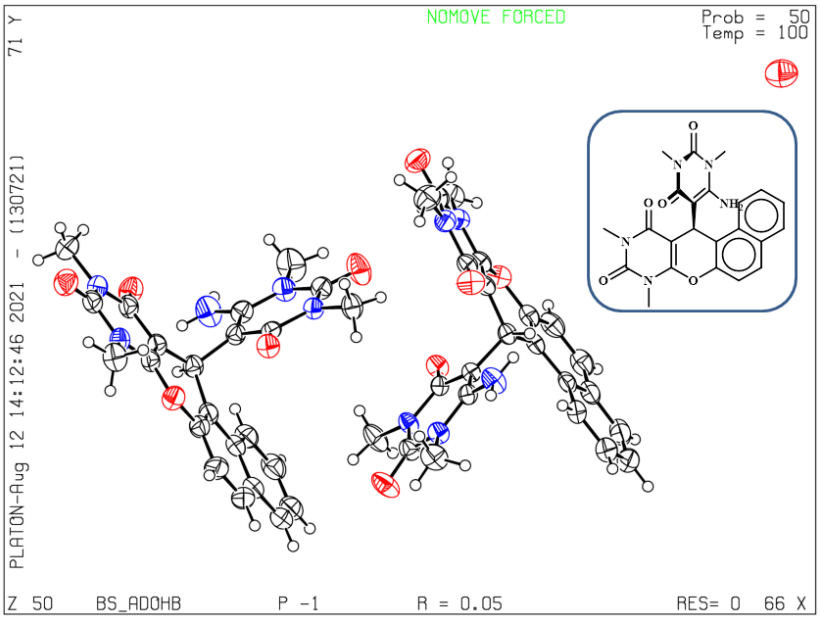
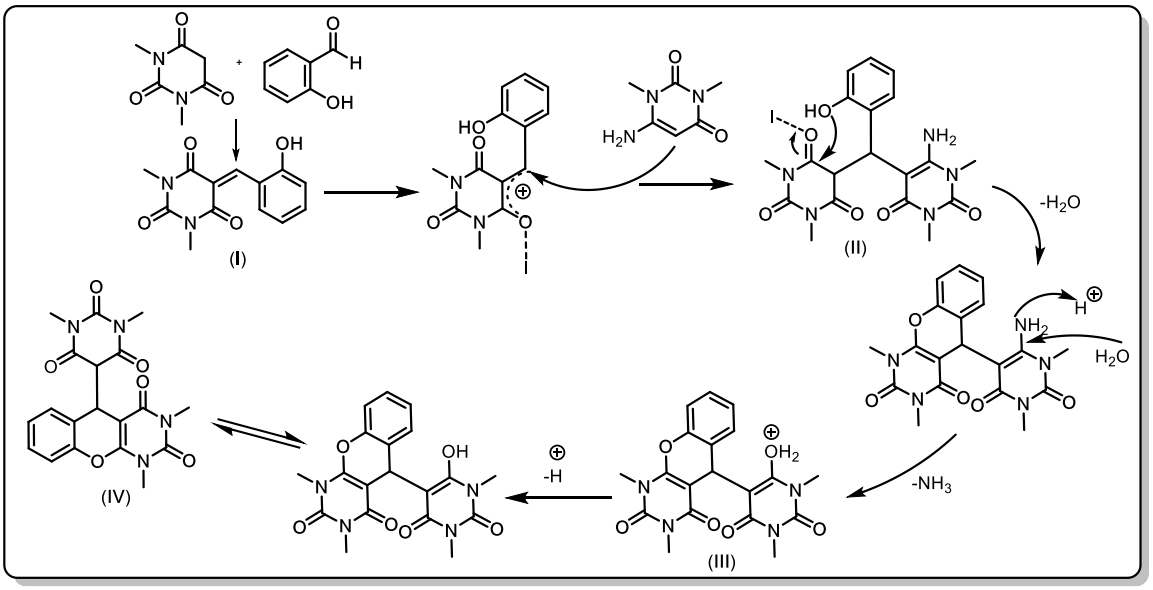


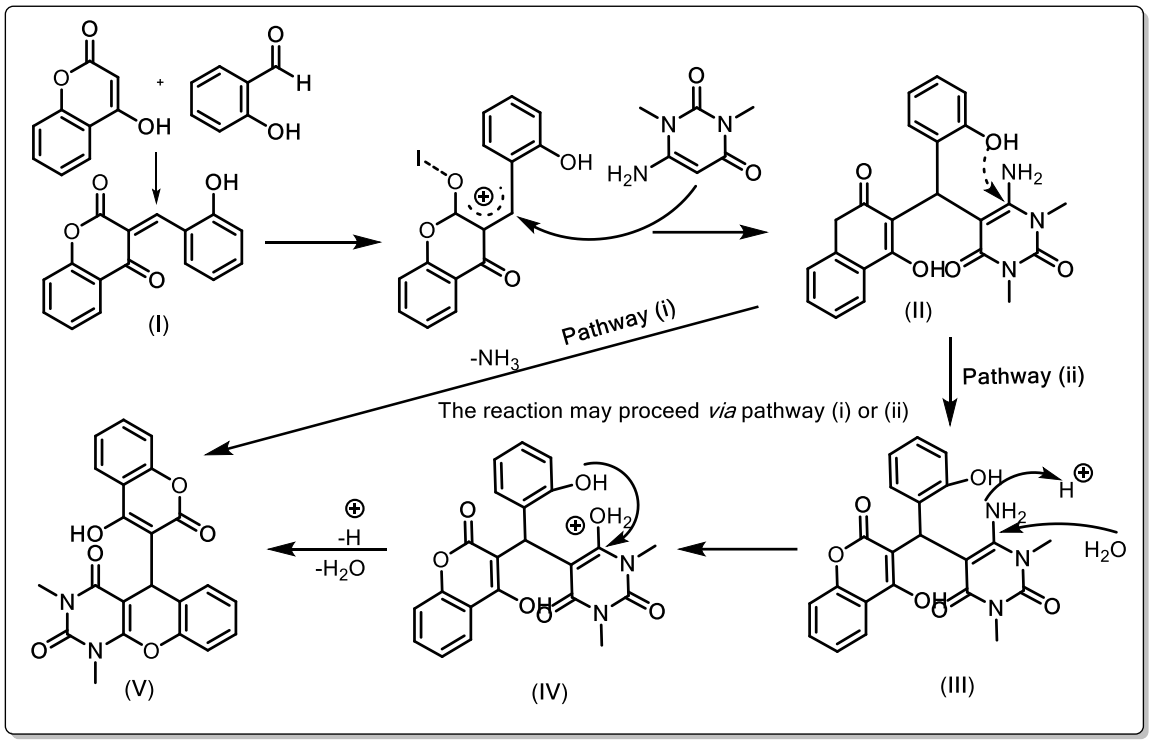
Figure 3.2.2 ORTEP diagram of **8b (CCDC depository number: 2124798)**

The plausible mechanism of all the four reaction protocols can be summarized in a way that includes the functional group transformation of the amine group at elevated temperatures and the changes that take place during the reaction carried out at room temperature. Under refluxing conditions (**scheme 3.2.11**, **3.2.13**, and **3.2.15**), the benzylidene moiety (**I**) formed after the Knoevenagel condensation between the barbituric acid or 4-hydroxycoumarin and the 2-hydroxybenzaldehydes is attacked by the nucleophillic 5-position of the 6-aminouracil, resulting in the formation of a tertiary methyl intermediate (**II**). Then, in the presence of the acid catalyst, the carbonyl group of the barbiturate part undergoes dehydrogenative cyclisation to form (**III**) and the amino group of the 6-

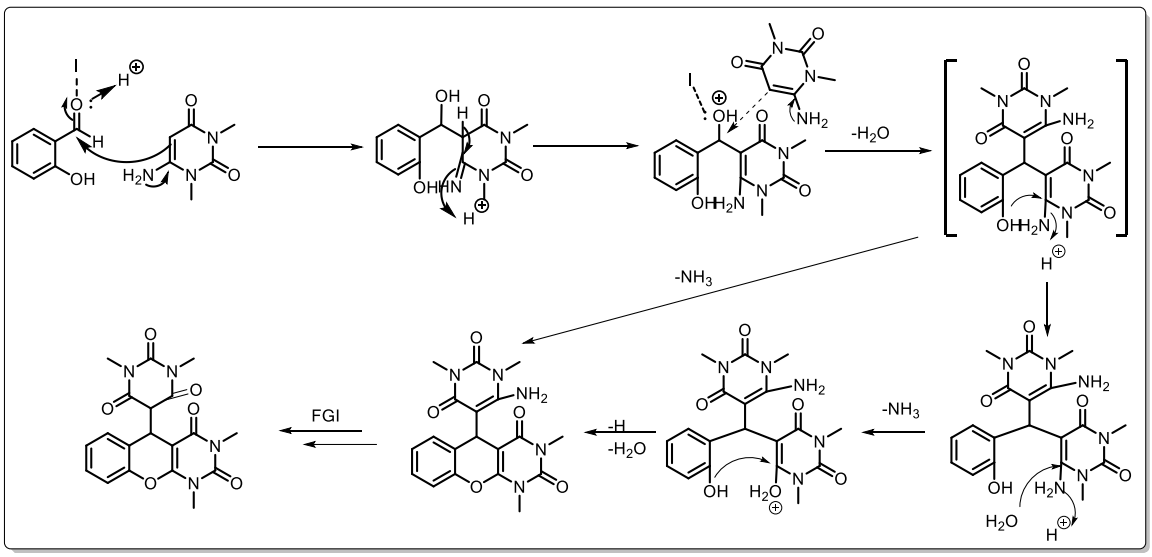
aminouracil undergoes transformation into a carbonyl group (**IV**). In case of 4-hydroxycoumarin, after the formation of the tertiary methyl intermediate (**II**), the amino group undergoes the transformation into a carbonyl group, after which the cyclisation step takes place to form the product (**V**). When the reaction discussed in **scheme 3.2.16** and **3.2.17** take place at room temperature, then no functional group transformation takes place and the reaction simply proceeds *via* deaminative cyclisation. In addition to this, the role of the catalyst and the additive can also be observed in the plausible mechanism. While iodine molecule aids in increasing the nucleophilicity of the aldehyde carbonyl or the benzylidene centre, the presence of the additive, acetic acid, aids the removal of the groups during the condensation steps. The plausible mechanism is shown in **schemes 3.2.18 - 3.2.21**.



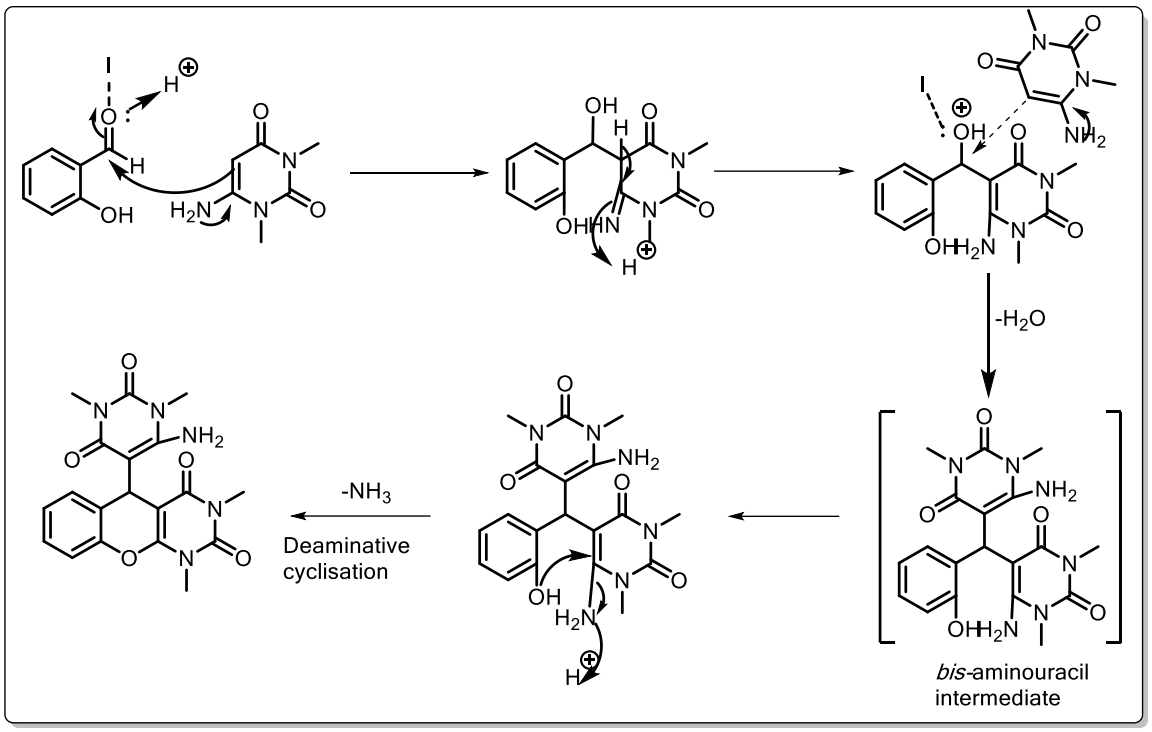
Scheme 3.2.18 Plausible mechanism for the formation of barbiturate functionalised chromeno[2,3-*d*]pyrimidines *via* I_2-acetic acid catalysed MCR between barbituric acid, 6-aminouracil and 2-hydroxybenzaldehyde



Scheme 3.2.19 Plausible mechanism for the formation of 4-hydroxycoumarin functionalised chromeno[2,3-*d*]pyrimidines *via* I_2-acetic acid catalysed MCR between 4-hydroxycoumarin, 6-aminouracil and 2-hydroxybenzaldehyde



Scheme 3.2.20 Plausible mechanism for I_2-acetic acid catalysed synthesis of barbiturate functionalised chromeno[2,3-*d*]pyrimidines *via* reaction between 6-aminouracil and 2-hydroxybenzaldehyde under reflux conditions



Scheme 3.2.21 Plausible mechanism for I_2-acetic acid catalysed synthesis of 6-aminouracil functionalised chromeno[2,3-*d*]pyrimidines *via* reaction between 6-aminouracil and 2-hydroxybenzaldehyde at room temperature

3.2.3 EXPERIMENTAL SECTION

General Information

All reagents were purchased from commercial sources and used as received, without any purification. Commercially available solvents were distilled before the reactions and water used for reaction as well as during work up was double distilled prior to use. ^{1}H and ^{13}C NMR spectra of the products were recorded with a JNM ECS 400 MHz NMR spectrophotometer (JEOL) using deuterated chloroform ($CDCl_3$) ($CDCl_3$, δ= 7.26ppm, singlet, for ^{1}H and 76.98 ppm, triplet, for ^{13}C) as the solvent and Tetramethylsilane (TMS δ= 0.00 ppm, singlet, for ^{1}H and 0.0 ppm, singlet, for ^{13}C) as the internal standard and deuterated dimethyl sulphoxide (DMSO-D_6, δ= 2.46ppm, quintet, for ^{1}H and 40.0 ppm, septet, for ^{13}C)

as the solvent as well as the internal standard. Due to the presence of HOD in $CDCl_3$ an additional signal at 1.59 ppm is observed in the ^1H spectrum. Similarly additional signal at 3.30 ppm, in ^1H NMR spectra, is seen because of the presence of HOD in DMSO-D_6. Chemical shift values are expressed in ppm. Coupling constants (*J*) are expressed in Hertz (Hz). The signals are reported as "s"= singlet, "d"= doublet, "t"= triplet, and "m"= multiplet. HRMS data were recorded by electrospray ionization with a Q-TOF mass analyzer. X-ray reflections were collected on a Bruker APEX-II, CCD diffractometer using Mo Kα (λ= 0.71073 Å). Data reduction was performed using Bruker SAINT software. Reactions were monitored by thin-layer chromatography using aluminium sheets with silica gel $60F_{254}$ (Merck). UV light and Iodine vapors were used as visualizer.

General Procedure for the synthesis of 5-(2,4-dioxo-1,3,4,4a,5,10a-hexahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-pyrimidine-2,4,6(1*H*,3*H*,5*H*)-triones and 5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-diones. (4aa-aj, 4ba, 4bb, 4bh, 4bj, 4ca, 4cc and 7da-df) (barbiturate/4-hydroxycoumarin functionalised chromeno[2,3-*d*]pyrimidine)

Method A (three component reaction)

Barbituric acid/4-hydroxycoumarin (1 equiv), 2-hydroxybenzaldehydes (1 equiv), and *N,N'*-dimethyl-6-aminouracil (1 equiv) were mixed in 5 mL distilled water to form a slurry. To this mixture 10 mol% each of molecular iodine and acetic acid was added and the reaction mixture was stirred under reflux for 30 minutes. After the completion of the reaction, the reaction mixture was cooled and the solid

product was collected by filtration. The product was washed with DCM, ethanol and water, after which it was dried under vacuum.

Method B (two component reaction)

2-hydroxybenzaldehydes (1 equiv), and *N,N'*-dimethyl-6-aminouracil (2 equiv) were mixed in 5 mL distilled water to form a slurry. To this mixture 10 mol% each of molecular iodine and acetic acid was added and the reaction mixture was stirred under reflux for 30 minutes. After the completion of the reaction, the reaction mixture was cooled and the solid product was collected by filtration. The product was washed with DCM, ethanol and water, after which it was dried under vacuum.

General Procedure for the synthesis of 5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-diones (8a-j) (6-aminouracil functionalized chromeno[2,3-*d*]pyrimidines)

2-hydroxybenzaldehydes (1 equiv), and *N,N'*-dimethyl-6-aminouracil (2 equiv) were mixed in 5 mL distilled water to form a slurry. To this mixture 10 mol% each of molecular iodine and acetic acid was added and the reaction mixture was stirred at room temperature for 15 minutes. After the completion of the reaction, the reaction mixture was cooled and the solid product was collected by filtration. The product was washed with DCM, ethanol and water, after which it was dried under vacuum.

Procedure for crystallisation of 7df

0.100 g of 7df was dissolved in a 3 mL mixture of CH_3NO_2 and DCM (1:1) and kept aside in the dark at 10 °C for a period of 2 days. The crystals thus formed were analysed *via* single crystal X-ray diffraction.

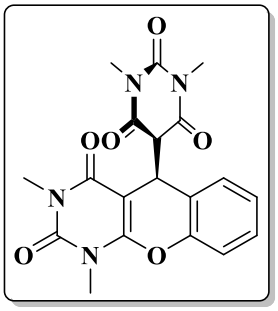
Procedure for crystallisation of 8b

0.100 g of 8b was dissolved in a 3 mL mixture of CH_3NO_2, DCM and DMSO (1:1:1) and kept aside in the dark at room temperature for a period of 4 days. The crystals thus formed were analysed *via* single crystal X-ray diffraction.

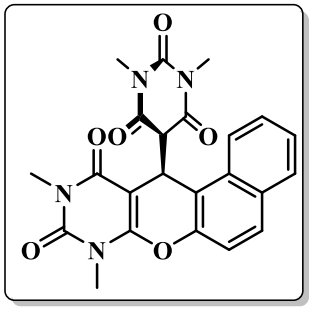
3.2.4 CONCLUSION

In conclusion, it can be said that the utilisation of molecular iodine in combination with acetic acid as a catalytic system was efficiently done for developing four reaction protocols towards the synthesis of three different classes of compounds, namely, barbiturate functionalised chromeno[2,3-*d*]pyrimidines, 4-hydroxycoumarin functionalised chromeno[2,3-*d*]pyrimidines, and 6-aminouracil functionalised chromeno[2,3-*d*]pyrimidines. The reaction protocols were successfully accomplished on-water and high selectivity of the products was achieved. The products formed were solid and isolated with high purity *via* chromatography free methods i.e. by simple filtration and washing with the appropriate solvents followed by drying. Additionally, the methods developed were green, operationally simple and safe.

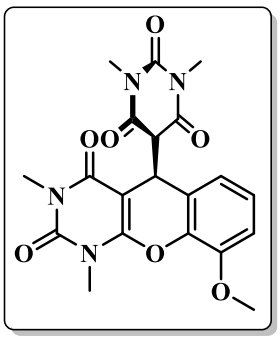
3.2.5 CHARACTERISATION DATA OF THE PRODUCTS



5-(1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4aa) Deep yellow solid (Method A: 373.89 mg, Method B: 374.56 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.36-7.29 (m, 1H), 7.17-7.11 (m, 3H), 5.29 (d, *J*= 2.5 Hz, 1H), 4.13 (d, *J*= 2.5 Hz, 1H), 3.51 (s, 3H), 3.36 (s, 3H), 3.27 (s, 3H), 3.03 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 167.8, 162.4, 154.5, 151.5, 150.9, 149.4, 129.2, 127.7, 126.3, 120.2, 116.5, 86.8, 54.2, 36.9, 29.8, 28.7, 28.5. **HRMS (+ESI)** calcd. for $C_{19}H_{18}N_4O_6$ $(M+H)^+$: 398.1226 found: 398.1239

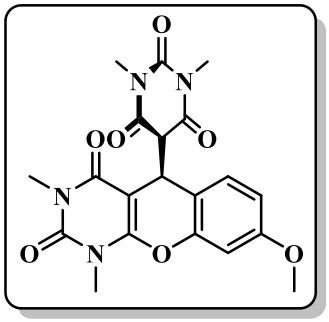


5-(8,10-dimethyl-9,11-dioxo-8,10,11,12-tetrahydro-9*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidin-12-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4ab) Orange solid (Method A: 394.78 mg, Method B: 393.96 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ8.53 (d, *J* = 7.9 Hz, 1H), 7.90 – 7.81 (m, 2H), 7.70 (t, *J* = 8.5 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 5.63 (d, *J* = 1.5 Hz, 1H), 3.93 (d, *J* = 1.5 Hz, 1H), 3.57 (s, 3H), 3.32 (d, *J* = 1.5 Hz, 6H), 3.04 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 167.8, 167.5, 162.4, 154.8, 151.4, 150.5, 148.0, 131.9, 130.5, 130.1, 129.3, 128.4, 122.9, 116.3, 114.6, 85.7, 53.9, 35.5, 29.5, 28.8, 28.3. **HRMS (+ESI)** calcd. for $C_{23}H_{20}N_4O_6$ $(M+H)^+$: 448.1383 found: 448.1389



5-(9-methoxy-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4ac)

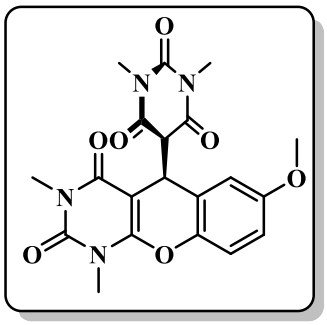
Yellow solid (Method A: 402.89 mg, Method B: 402.56 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.31 (s, 1H), 7.01 (s, 1H), 6.90 (s, 1H), 5.21 (d, *J*= 2.0 Hz, 1H), 4.13 (d, *J*= 2.0 Hz, 1H), 3.83-3.76 (m, 3H), 3.59 (s, 3H), 3.31 (s, 3H), 3.12 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 169.5, 163.3, 158.5, 155.1, 143.2, 141.5, 138.3, 124.8, 123.6, 118.2, 115.2, 104.5, 67.6, 59.4, 37.7, 32.3, 31.2, 29.5. **HRMS (+ESI)** calcd. For $C_{20}H_{20}N_4O_7$ $(M+H)^+$: 428.1332 found: 428.1345



5-(8-methoxy-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4ad)

(Method A: 403.10 mg, Method B: 385.28 mg)

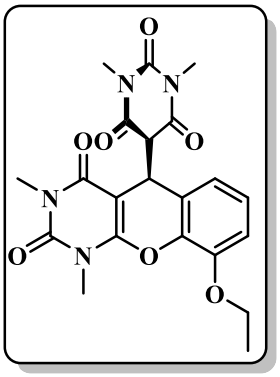
^{1}H NMR (400 MHz, Chloroform-*D*) δ 7.68 (s, 1H), 6.79-6.73 (m 2H), 5.56 (s, 1H), 3.95 (d, *J*= 1.5 Hz, 1H), 4.02 (d, *J*= 1.5 Hz, 1H), 3.81 (s, 3H), 3.62 (s, 3H), 3.40 (s, 6H), 3.10 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 167.1, 166.9, 161.3, 161.4, 154.2, 152.8, 151.1, 147.3, 130.8, 113.3, 113.4, 104.6, 103.4, 59.7, 56.0, 33.8, 30.4, 28.68, 26.7. **HRMS (+ESI)** calcd. For $C_{20}H_{20}N_4O_7$ $(M+H)^+$: 428.1332 found: 428.1351



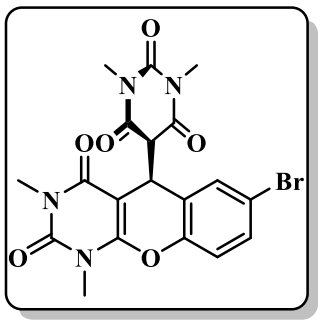
5-(7-methoxy-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4ae)

(Method A: 393.88 mg, Method B: 402.11 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.65 (s, 1H), 7.23-7.16 (m, 2H), 5.58 (d, *J*= 1.0 Hz, 1H), 4.06 (d, *J*= 1.5 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.29 (s, 6H), 2.95 (s, 3H). **^{13}C**

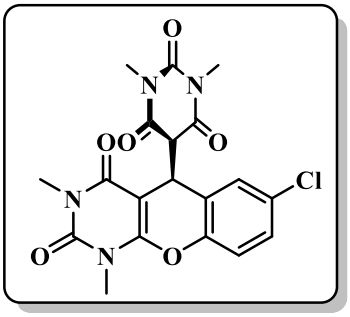
NMR (100 MHz, Chloroform-*D*) δ 168.0, 167.3, 159.4, 154.0, 152.8, 149.4, 142.6, 125.1, 120.1, 115.7, 115.2, 105.4, 61.7, 57.0, 37.2, 31.4, 28.6, 28.1. **HRMS (+ESI)** calcd. For $C_{20}H_{20}N_4O_7$ $(M+H)^+$: 428.1332 found: 428.1349



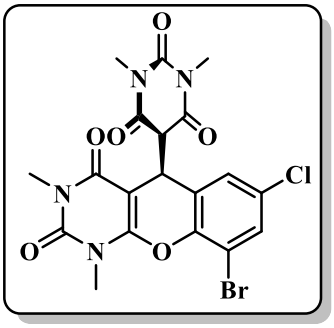
5-(9-ethoxy-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4af) Pale yellow solid (Method A: 398.11 mg, Method B: 407.05 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.59-7.46 (m, 3H), 5.01 (d, *J*= 2.5 Hz, 1H), 4.49 – 4.41 (m, 3H), 3.31 (s, 3H), 3.27 (s, 3H), 2.92 (s, 6H), 1.53 (d, *J*= 2.5 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 169.0, 164.7, 158.0, 154.8, 152.5, 149.4, 143.2, 129.9, 127.2, 124.1, 122.0, 103.0, 66.2, 61.7, 38.9, 35.1, 31.6, 28.17, 17.2. **HRMS (+ESI)** calcd. for $C_{21}H_{22}N_4O_7$ $(M+H)^+$: 442.1488 found: 442.1501



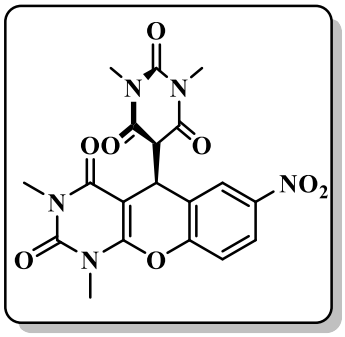
5-(7-bromo-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4ag) (Method A: 428.56 mg, Method B: 418.90 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.82 (s, 1H), 7.33 (d, *J*= 7.8 Hz, 1H), 6.77 (d, *J*= 7.8 Hz, 1H), 5.45 (s, 1H), 3.99 (s, 1H), 3.61 (s, 3H), 3.25 (s, 6H), 2.95 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 165.0, 161.3, 158.0, 156.8, 151.4, 150.1, 137.0, 137.3, 129.4, 124.8, 124.4, 107.4, 64.7, 39.2, 35.4, 30.6, 29.1. **HRMS (+ESI)** calcd. For $C_{19}H_{17}BrN_4O_6$ $(M+H)^+$: 476.0331 found: 476.0347



5-(7-chloro-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-d]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4ah) (Method A: 393.66 mg, Method B: 384.96 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.65 (s, 1H), 7.17 (d, *J*= 8.2 Hz, 1H), 6.88 (d, *J*= 8.2 Hz, 1H), 5.47 (d, *J*= 1.2 Hz, 1H), 4.09 (d, *J*= 1.2 Hz, 1H), 3.64 (s, 3H), 3.28 (s, 6H), 2.95 (m, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 166.5, 165.7, 162.2, 157.2, 153.3, 151.3, 135.2, 133.4, 130.7, 129.6, 123.6, 108.7, 64.7, 39.3, 35.1, 31.8, 29.1. **HRMS (+ESI)** calcd. For $C_{19}H_{17}ClN_4O_6$ $(M+H)^+$: 432.0837 found: 432.0855

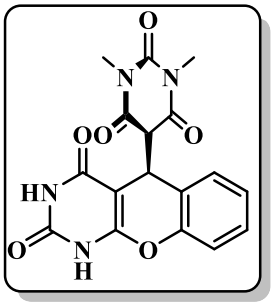


5-(9-bromo-7-chloro-1,3-dimethyl-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4ai) Pale yellow solid (Method A: 448.13 mg, Method B: 447.83 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.68 (s, 1H), 7.54 (s, 1H), 5.27 (d, *J*= 2.5 Hz, 1H), 4.35 (d, *J*= 2.5 Hz, 1H), 3.44 (s, 3H), 3.12(s, 3H), 2.97 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 164.0, 162.3, 158.02, 155.2, 149.5, 145.1, 136.0, 132.2, 131.9, 129.5, 119.0, 104.8, 62.7, 38.4, 33.4, 30.6, 28.7. **HRMS (+ESI)** calcd. for $C_{19}H_{16}BrClN_4O_6$ $(M+H)^+$: 509.9942 found: 509.9958

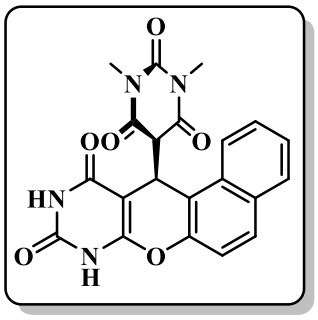


5-(1,3-dimethyl-7-nitro-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4aj) Deep yellow solid (Method A: 399.24 mg, Method B: 399.02 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 8.54 (s, 1H), 8.00 (d, *J*= 8.2 Hz, 1H), 7.46 (d, *J*= 7.8 Hz, 1H), 5.06 (d, *J*= 2.0 Hz, 1H), 4.12 (d, *J*= 2.0 Hz, 1H), 3.33 (s, 3H), 3.16 (s, 3H), 2.94 (s, 6H). **^{13}C NMR** (100 MHz, Chloroform-*D*)

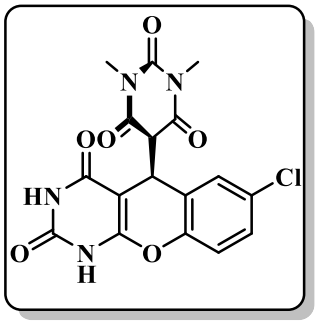
δ 167.0, 162.3, 158.2, 155.2, 153.2, 149.3, 147.1, 129.0, 127.2, 121.1, 118.3, 104.7, 59.6, 39.2, 32.4, 30.6, 29.7. **HRMS (+ESI)** calcd. for $C_{19}H_{17}N_5O_8$ $(M+H)^+$: 443.1077 found: 443.1086



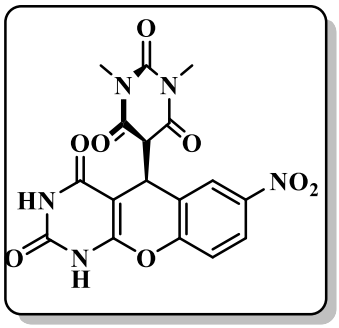
5-(2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4ba) (347.86 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.15 (s, 1H), 11.01 (s, 1H), 7.61-7.51 (m, 4H), 5.13 (s, 1H), 4.06 (s, 1H), 3.59 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 171.5, 163.4, 159.2, 150.8, 147.3, 142.8, 134.3, 132.7, 126.7, 127.1, 115.9, 88.1, 54.7, 40.0, 29.1. **HRMS (+ESI)** calcd. For $C_{17}H_{14}N_4O_6$ $(M+H)^+$: 370.0913 found: 370.0936



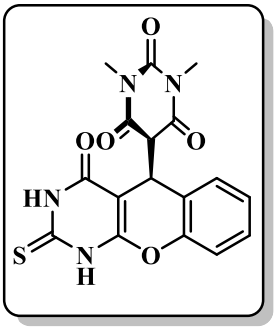
5-(9,11-dioxo-8,10,11,12-tetrahydro-9*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidin-12-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4bb) (369.75 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.20 (s, 1H), 10.95 (s, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 7.98-7.93 (m, 2H), 7.67 (t, *J* = 7.7 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 9.0 Hz, 1H), 5.25 (s, 1H), 3.74 (d, *J* = 0.9 Hz, 1H), 3.39 (s, 3H), 3.13 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 170.5, 169.8, 162.0, 154.7, 151.0, 150.4, 147.7, 132.1, 131.3, 131.0, 130.5, 129.4, 115.8, 85.4., 53.9, 41.9, 29.3. **HRMS (+ESI)** calcd. For $C_{21}H_{16}N_4O_6$ $(M+H)^+$: 420.1070 found: 420.1085



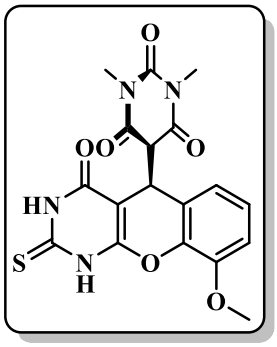
5-(7-chloro-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4bh) (363.90 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.13 (s, 1H), 11.05 (s, 1H), 7.65 (s, 1H), 7.17 (d, *J*= 8.0 Hz, 1H), 6.83 (d, *J*= 8.0 Hz, 1H), 5.13 (d, *J*= 1.5 Hz, 1H), 3.82 (d, *J*= 1.5 Hz, 1H), 3.26 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 172.2, 168.1, 157.8, 155.6, 149.9, 144.7, 135.2, 133.3, 129.8, 123.1, 88.1, 54.6, 39.8, 29.1. **HRMS (+ESI)** calcd. For $C_{17}H_{13}ClN_4O_6$ $(M+H)^+$: 404.0524 found: 404.0537



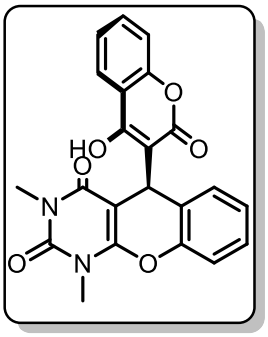
1,3-dimethyl-5-(7-nitro-2,4-dioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4bj) (369.35 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.25 (s, 1H), 10.98 (s, 1H), 8.41 (s, 1H), 8.03 (d, *J*= 8.2 Hz, 1H), 7.25 (d, *J*= 7.8 Hz, 1H), 5.17 (s, 1H), 3.86 (s, 1H), 3.59 (s, 3H), 3.29 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 174.07, 169.1, 159.8, 155.6, 153.8, 148.6, 144.7, 132.4, 128.2, 123.3, 115.9, 86.1, 59.6, 35.8, 30.1. **HRMS (+ESI)** calcd. For $C_{17}H_{13}N_5O_8$ $(M+H)^+$: 415.0764 found: 415.0777



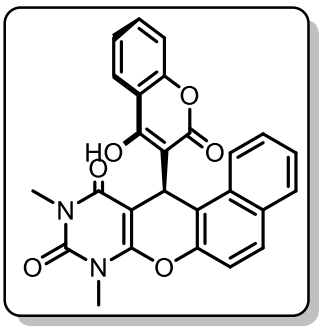
1,3-dimethyl-5-(4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4ca) (339.89 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.25 (s, 1H), 11.11 (s, 1H), 7.63-7.54 (m, 4H), 5.19 (s, 1H), 4.16 (s, 1H), 3.63 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.6, 175.1, 160.1, 154.2, 149.3, 142.1, 133.1, 130.8, 125.7, 124.1, 117.8, 98.0, 61.7, 37.0, 29.8. **HRMS (+ESI)** calcd. For $C_{17}H_{14}N_4O_5S$ $(M+H)^+$: 386.0685 found: 386.0703



5-(9-methoxy-4-oxo-2-thioxo-1,3,4,5-tetrahydro-2*H*-chromeno[2,3-*d*]pyrimidin-5-yl)-1,3-dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (4cc) (374.50 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.19 (s, 1H), 11.10 (s, 1H), 8.06 (d, *J*= 8.0 Hz, 1H), 7.56-7.49 (m, 1H), 6.86 (d, *J*= 7.8 Hz, 1H), 5.10 (s, 1H), 4.06 (s, 1H), 3.87 (s, 3H), 3.21 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 181.6, 179.5, 160.1, 155.2, 151.7, 143.6, 141.5, 128.3, 126.5, 124.2, 120.3, 91.5, 55.6, 53.9, 31.2, 28.1. **HRMS (+ESI)** calcd. For $C_{18}H_{16}N_4O_6S$ $(M+H)^+$: 416.0791 found: 416.0811

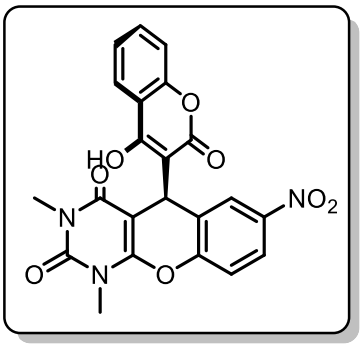


5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (7da) Yellow solid (372.14 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.40 (d, *J*= 7.8 Hz, 1H), 7.38-7.32 (m, 2H), 7.23 (d, *J* = 7.6 Hz, 2H), 7.07 (d, *J*= 7.8 Hz, 1H), 6.93-6.87 (m, 3H), 5.23 (s, 1H), 3.70 (s, 3H), 3.36 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 165.5, 163.2, 160.3, 152.2, 151.7, 148.8, 146.5, 134.7, 131.7, 130.8, 126.6, 122.5, 121.9, 115.6, 114.4, 106.3, 65.2, 30.4, 29.6. **HRMS (+ESI)** calcd. For $C_{22}H_{16}N_2O_6$ $(M+H)^+$: 404.1008 found: 404.1022

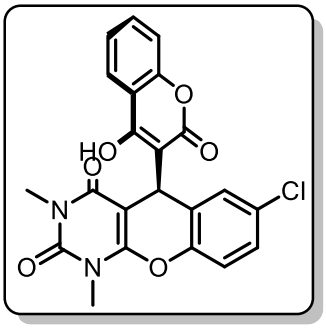


12-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-8,10-dimethyl-8,12-dihydro-9*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-dione (7db) Deep yellow solid (363.76 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 8.25 (d, *J*= 8.0 Hz, 1H), 7.68 (d, *J*= 7.8 Hz, 1H), 7.41-7.33 (m, 3H), 7.33 (d, *J* = 7.4 Hz, 2H), 7.19-7.12 (m, 3H), 5.41 (s, 1H), 3.68 (s, 3H), 3.39 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 167.5, 162.2, 157.3, 154.2, 153.7, 150.6, 144.5, 133.2, 132.7, 131.7, 127.8, 127.3, 126.7,

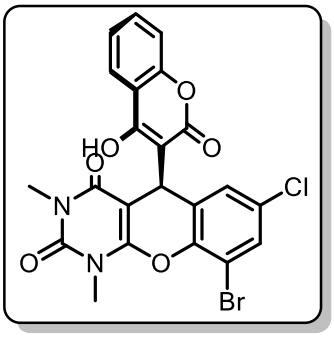
125.5, 125.3, 124.6, 124.1, 117.9, 117.1, 116.5, 116.3, 105.4, 62.4, 30.9, 29.6. **HRMS (+ESI)** calcd. For $C_{26}H_{18}N_2O_6$ $(M+H)^+$: 454.1165 found: 454.1179



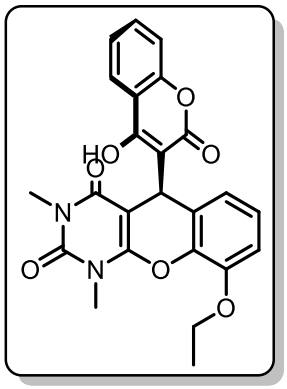
5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-7-nitro-1,5-dihydro-2H-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (7dc) Deep red solid (386.58 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 8.09 (s, 1H), 7.97 (d, *J*= 8.2 Hz, 1H), 7.60 (d, *J*= 8.0 Hz, 1H), 7.43 (d, *J*= 7.8 Hz, 1H), 7.23-7.15 (m, 3H), 5.17 (s, 1H), 3.73 (s, 3H), 3.40 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 167.8, 164.2, 162.3, 159.2, 158.7, 154.0, 152.0, 149.8, 137.7, 126.7, 124.1, 123.8, 120.1, 119.1, 117.0, 116.8, 108.3, 67.5, 31.1, 29.6. **HRMS (+ESI)** calcd. For $C_{22}H_{15}N_3O_8$ $(M+H)^+$: 449.0859 found: 449.0871



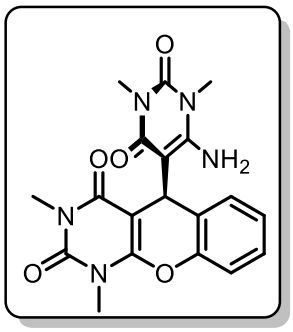
7-chloro-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (7dd) Yellow solid (390.03 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.78 (s, 1H), 7.46 (d, *J*= 7.8 Hz, 1H), 7.42-7.38 (m, 2H), 7.34 (d, *J*= 7.8 Hz, 1H), 7.16 (d, *J*= 8.0 Hz, 1H), 6.96 (d, *J*= 7.8 Hz, 1H), 5.41 (s, 1H), 3.56 (s, 3H), 3.42 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 165.5, 162.2, 161.3, 158.2, 155.7, 152.0, 146.6, 135.7, 132.7, 130.0, 128.2, 126.7, 124.8, 121.0, 119.1, 117.3, 106.3, 59.5, 30.8, 29.4. **HRMS (+ESI)** calcd. For $C_{22}H_{15}ClN_2O_6$ $(M+H)^+$: 438.0619 found: 438.0633



9-bromo-7-chloro-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (7de) Deep yellow solid (433.05 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.56 (d, *J* = 8.0 Hz, 1H), 7.42 – 7.40 (m, 2H), 7.29 (s, 1H), 7.17 (s, 1H), 7.10 (d, *J*= 7.8 Hz, 1H), 5.28 (s, 1H), 3.76 (s, 3H), 3.46 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 165.8, 164.4, 162.5, 158.0, 155.7, 151.1, 144.2, 134.7, 133.6, 133.3, 130.3, 128.9, 125.6, 124.9, 119.3, 118.1, 116.5, 108.3, 59.3, 33.1, 30.6. **HRMS (+ESI)** calcd. For $C_{22}H_{14}BrClN_2O_6$ $(M+H)^+$: 515.9724 found: 515.9739

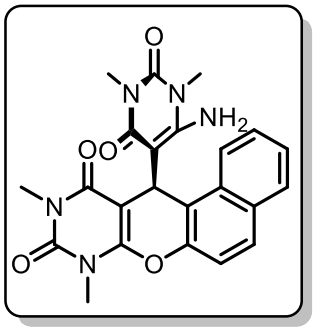


9-ethoxy-5-(4-hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (7df) Orange solid (384.99 mg)**^{1}H NMR** (400 MHz, Chloroform-*D*) δ 8.06 (d, *J* = 8.0 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.27 (d, *J* = 8.4 Hz, 1H), 7.04 (t, *J* = 8.0 Hz, 1H), 6.88 (d, *J* = 8.2 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.33 (s, 1H), 4.14 (q, *J* = 7.0, 2H), 3.65 (s, 3H), 3.40 (s, 3H), 1.46 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 165.3, 164.8, 164.2, 160.3, 160.0, 155.1, 152.7, 151.1, 146.7, 140.7, 124.5, 121.9, 119.9, 116.8, 116.0, 113.6, 113.1, 108.1, 65.1, 30.0, 29.9, 29.5, 29.1, 14.7. **HRMS (+ESI)** calcd. For $C_{24}H_{20}N_2O_7$ $(M+H)^+$: 448.1271 found: 448.1298

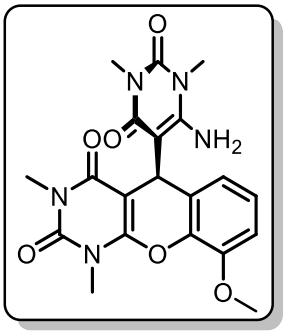


5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3-dimethyl-1,5-dihydro-2H-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (8a) Orange solid (372.98 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.68 (d, *J*= 8.0 Hz, 1H), 7.49-7.42 (m, 2H), 6.89 (d, *J* = 8.4 Hz, 1H), 5.80 (s, br, 2H), 5.26 (s, 1H), 3.68 (s, 3H), 3.50 (s, 3H), 3.26 (s, 3H), 2.89 (s, 3H).

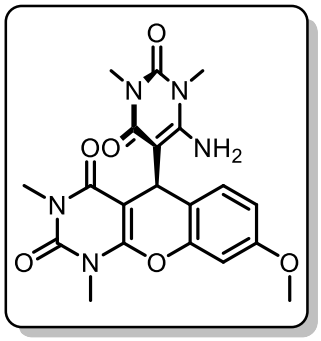
^{13}C NMR (100 MHz, Chloroform-*D*) δ 164.2, 162.1, 156.1, 155.2, 153.8, 151.6, 147.8, 129.2, 128.3, 125.6, 122.3, 117.2, 98.8, 69.4, 62.3, 31.1, 28.4. **HRMS (+ESI)** calcd. For $C_{19}H_{19}N_5O_5$ $(M+H)^+$: 397.1386 found: 397.1405



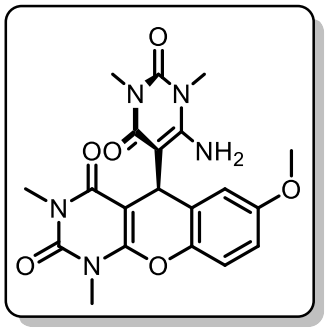
12-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-8,10-dimethyl-8,12-dihydro-9*H*-benzo[5,6]chromeno[2,3-*d*]pyrimidine-9,11(10*H*)-dione (8b) Red solid (380.21 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.84 – 7.75 (m, 3H), 7.50 (t, *J* = 6.9 Hz, 1H), 7.46 – 7.41 (m, 1H), 7.34 (d, *J* = 9.0 Hz, 1H), 6.04 (s, 2H), 5.38 (s, 1H), 3.64 (s, 3H), 3.53 (s, 3H), 3.38 (s, 3H), 3.01 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 164.3, 161.3, 154.3, 151.3, 151.0, 150.5, 148.7, 131.5, 131.1, 129.0, 128.9, 127.3, 125.0, 122.9, 115.9, 115.8, 92.5, 88.1, 31.6, 29.4, 28.3. **HRMS (+ESI)** calcd. For $C_{23}H_{21}N_5O_5$ $(M+H)^+$: 447.1543 found: 447.1555



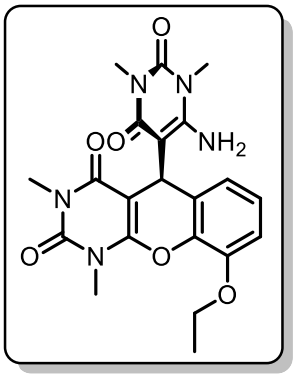
5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-9-methoxy-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (8c) Yellow solid (401.56 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.66 (d, *J*= 8.2 Hz, 1H), 7.16-11 (m, 1H), 7.05 (d, *J* = 8.2 Hz, 1H), 6.11 (s, br, 2H), 5.21 (s, 1H), 3.86 (s, 3H), 3.49 (s, 3H), 3.21 (s, 3H), 2.94 (s, 3H), 2.86 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 162.8, 161.5, 154.5, 154.1, 153.8, 150.3, 147.8, 138.6, 126.5, 125.9, 121.5, 115.1, 101.7, 68.8, 63.7, 56.2, 30.9, 28.5. **HRMS (+ESI)** calcd. For $C_{20}H_{21}N_5O_6$ $(M+H)^+$: 427.1492 found: 427.1515



5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-8-methoxy-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (8d) Yellow solid (376.20 mg)**^{1}H NMR (8d)** (400 MHz, Chloroform-*D*) δ 7.65 (s, 1H), 6.53-6.47 (m, 2H), 6.04 (s, br, 2H), 4.97 (s, 1H), 3.84 (s, 3H), 3.65 (s, 3H), 3.39 (s, 3H), 3.09 (s, 3H), 2.90 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 166.2, 162.1, 161.4, 156.1, 155.2, 154.3, 152.8, 149.2, 128.7, 119.0, 114.7, 108.0, 99.8, 66.4, 62.3, 56.4, 31.4, 29.9. **HRMS (+ESI)** calcd. For $C_{20}H_{21}N_5O_6$ $(M+H)^+$: 427.1492 found: 427.1508

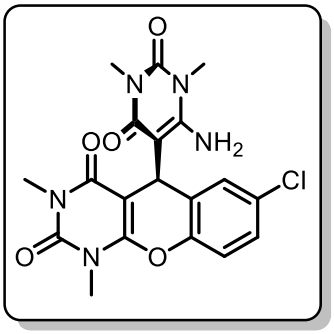


5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-7-methoxy-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (8e) Yellow solid (393.09 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.04 (d, *J* = 8.2 Hz, 1H), 6.94 (s, 1H), 6.83 (d, *J* = 8.2 Hz, 1H), 5.98 (s, br, 2H), 4.96 (s, 1H), 3.63 (s, 3H), 3.49 (s, 3H) 3.14 (s, 3H), 2.99 (s, 3H), 2.93 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 166.2, 162.3, 161.0, 156.1, 155.0, 154.6, 152.8, 145.7, 126.1, 121.4, 115.1, 109.1, 103.8, 70.9, 65.3, 54.4, 31.1, 29.9. **HRMS (+ESI)** calcd. For $C_{20}H_{21}N_5O_6$ $(M+H)^+$: 427.1492 found: 427.1522

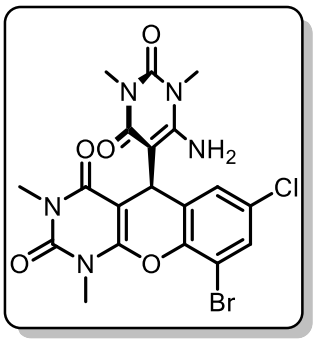


5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-9-ethoxy-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (8f) Deep yellow solid (397.12 mg)**^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.26 (d, *J* = 7.8 Hz, 1H), 6.85-6.79 (m, 2H), 6.12 (s, br, 2H), 4.93 (s, 1H), 4.14 (q, *J*= 7.4 Hz, 2H), 3.59 (s, 3H), 3.45 (s, 3H), 3.23 (s, 3H), 2.98 (s, 3H), 1.61 (t, *J*= 7 Hz, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*)

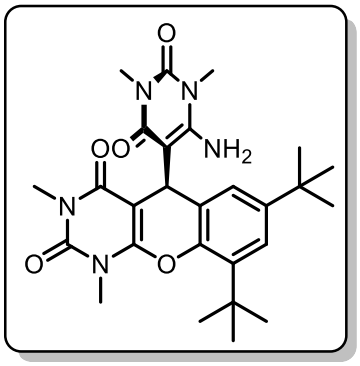
δ 164.2, 162.1, 155.9, 155.0, 154.3, 151.4, 149.1, 140.8, 127.0, 126.2, 122.1, 119.2, 101.7, 69.9, 65.2, 64.3, 31.4, 29.9, 15.8. **HRMS (+ESI)** calcd. For $C_{21}H_{23}N_5O_6$ $(M+H)^+$: 441.1648 found: 441.1672



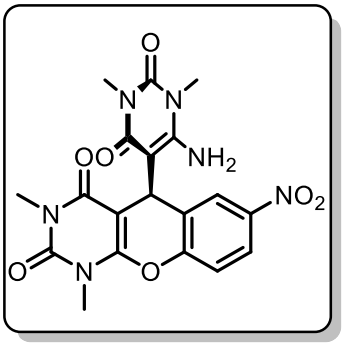
5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-7-chloro-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (8g) White solid (384.11 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.43 (s, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.2 Hz, 1H), 5.89 (s, br, 2H), 5.20 (s, 1H), 3.53 (s, 3H), 3.45 (s, 3H) 3.17 (s, 3H), 2.97 (s, 3H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 164.4, 162.6, 154.9, 154.0, 153.3, 151.3, 145.0, 129.6, 127.1, 125.1, 124.7, 118.7, 101.8, 70.9, 63.3, 30.5, 28.7. **HRMS (+ESI)** calcd. For $C_{19}H_{18}ClN_5O_5$ $(M+H)^+$: 431.0996 found: 431.1013



5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-9-bromo-7-chloro-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (8h) Pale yellow solid (438.01 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.06 (s, 1H), 7.00 (s, 1H), 5.98 (s, br, 2H), 5.19 (s, 1H), 3.68 (s, 3H), 3.52 (s, 3H) 3.18 (s, 3H), 2.97 (s, 3H),. **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 162.2, 161.1, 154.1, 154.0, 153.3, 150.4, 140.1, 130.6, 129.3, 127.8, 114.2, 100.6, 69.9, 63.3, 30.1, 28.9. **HRMS (+ESI)** calcd. For $C_{19}H_{17}BrClN_5O_5$ $(M+H)^+$: 509.0102 found: 509.0121



5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-7,9-di-tert-butyl-1,3-dimethyl-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (8i) Yellow solid (433.05 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 6.91 (s, 1H), 6.48 (s, 1H), 6.02 (s, br, 2H), 5.23 (s, 1H), 3.61 (s, 3H), 3.51 (s, 3H) 3.19 (s, 3H), 3.01 (s, 3H), 1.48 (s, 9H), 1.27 (s, 9H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 162.6, 161.5, 154.3, 154.2, 153.1, 150.3, 146.5, 145.7, 138.9, 125.2, 121.4, 120.6, 100.8, 69.9, 63.7, 36.5, 31.1, 31.3, 30.2, 28.4. **HRMS (+ESI)** calcd. For $C_{27}H_{35}N_5O_5$ $(M+H)^+$: 509.2638 found: 509.2647



5-(6-amino-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-1,3-dimethyl-7-nitro-1,5-dihydro-2*H*-chromeno[2,3-*d*]pyrimidine-2,4(3*H*)-dione (8j) Brown solid (389.08 mg) **^{1}H NMR** (400 MHz, Chloroform-*D*) δ 7.94 (s, 1H), 7.74 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 8.2 Hz, 1H), 5.89 (s, br, 2H), 5.10 (s, 1H). **^{13}C NMR** (100 MHz, Chloroform-*D*) δ 164.4, 161.8, 155.1, 154.0, 153.7, 151.4, 145.7, 127.6, 126.2, 121.3, 118.9, 108.8, 65.9, 62.3, 31.1, 29.9. **HRMS (+ESI)** calcd. For $C_{19}H_{18}N_6O_7$ $(M+H)^+$: 442.1237 found: 442.1254

3.2.6 REPRESENTATIVE NMR SPECTRA

Figure 3.2.3 ^{1}H NMR Spectrum of 4ab in Chloroform-*D*

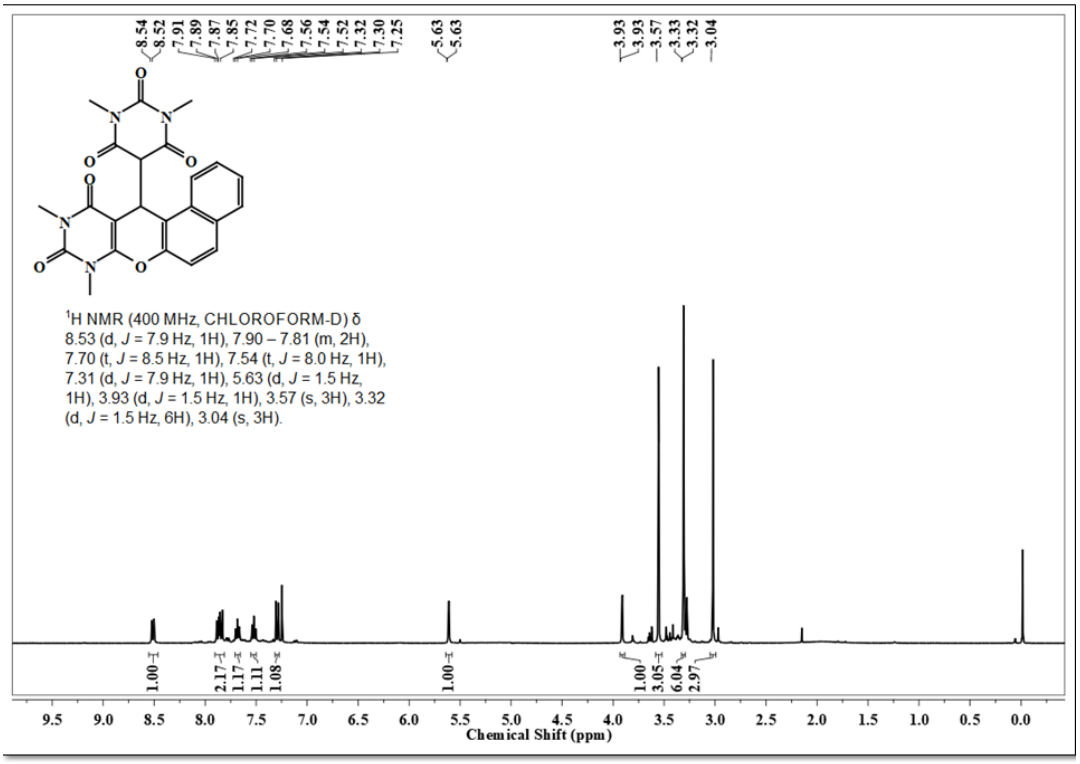


Figure 3.2.4 ^{13}C NMR Spectrum of 4ab in Chloroform-*D*

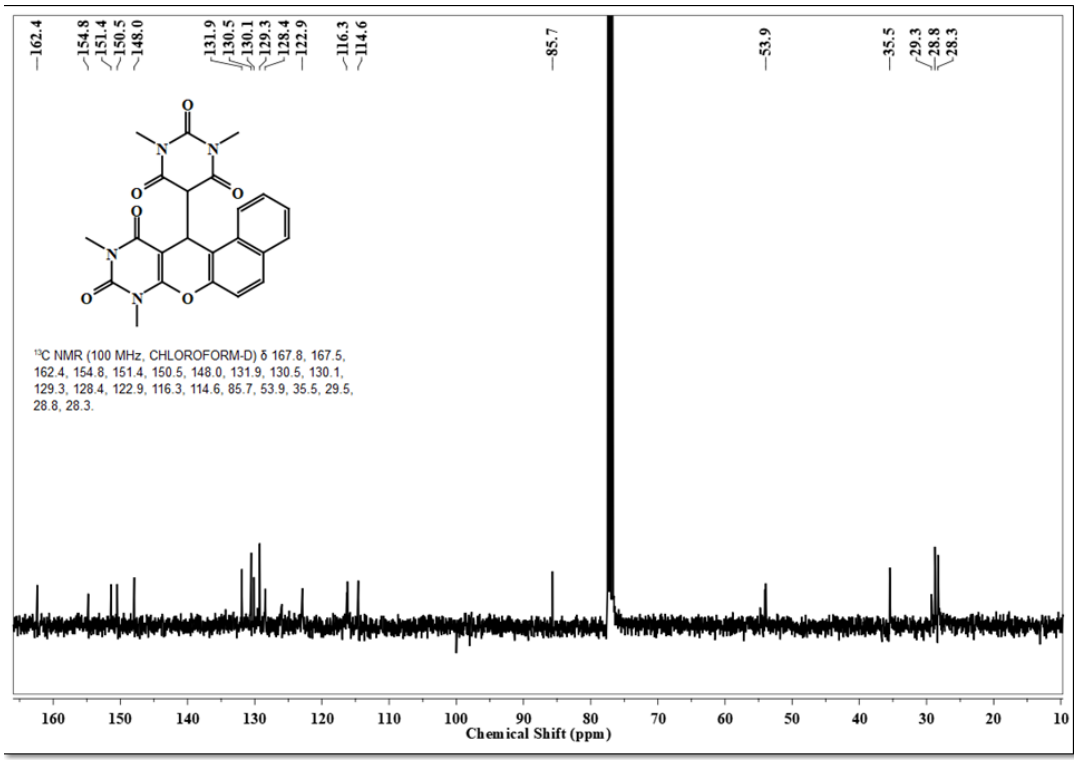


Figure 3.2.5 ^{1}H NMR Spectrum of 4bb in DMSO-*D*$_6$

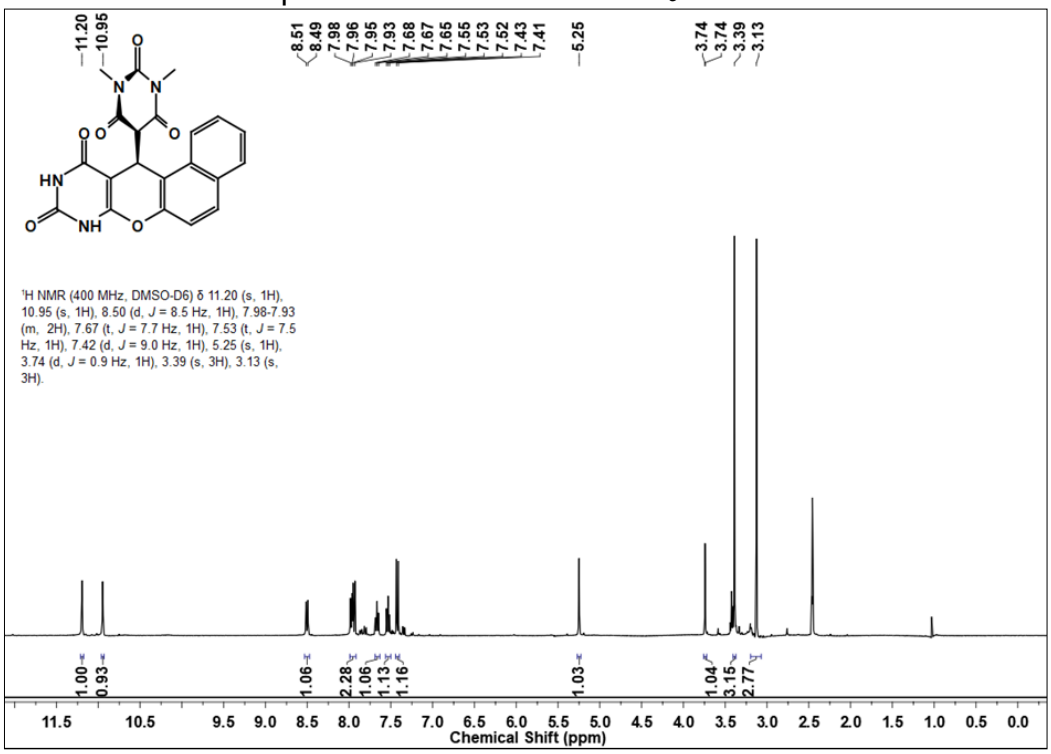


Figure 3.2.6 ^{13}C NMR Spectrum of 4ab in DMSO-*D*$_6$

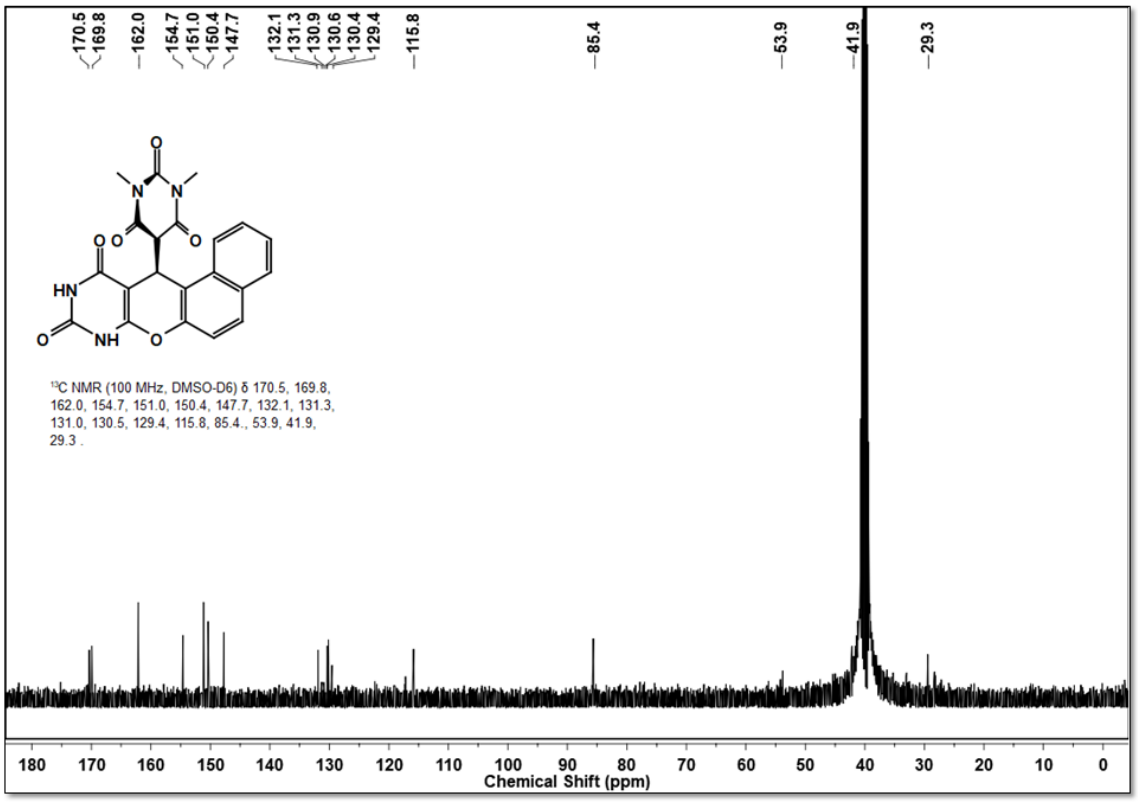


Figure 3.2.7 ^{1}H NMR Spectrum of 7df in Chloroform-*D*

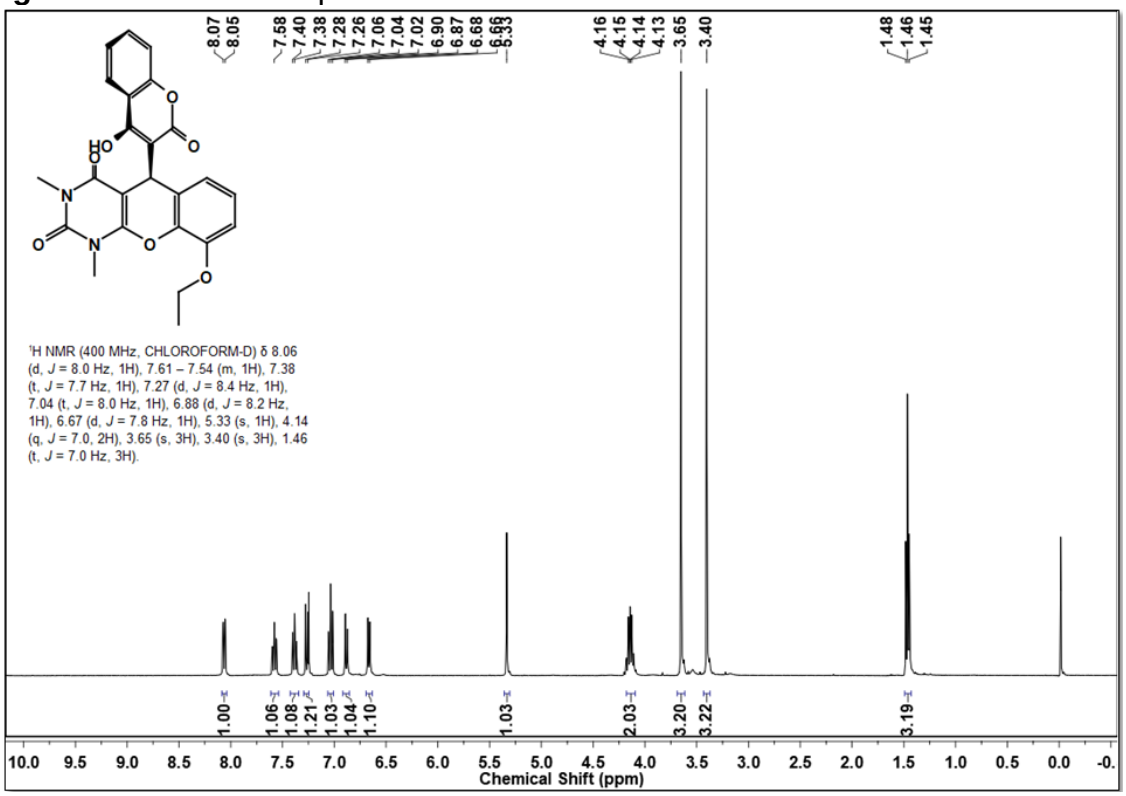


Figure 3.2.8 ^{13}C NMR Spectrum of 7df in Chloroform-*D*

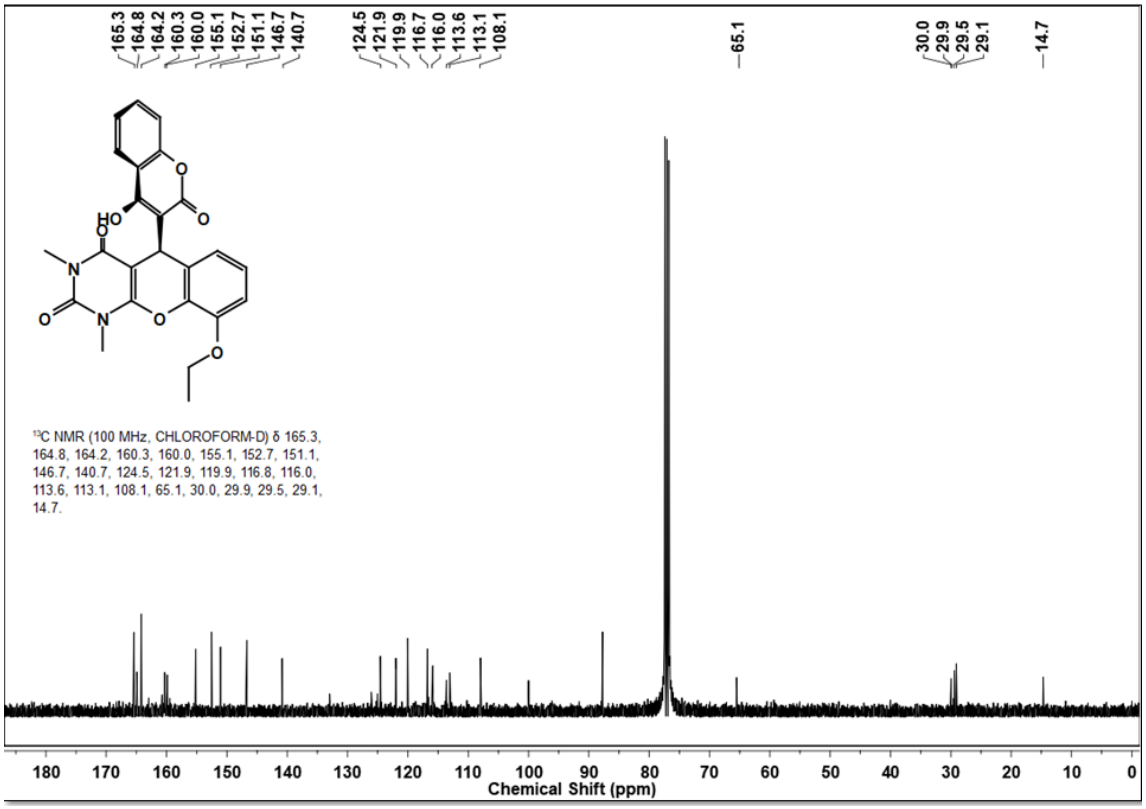


Figure 3.2.9 ^{1}H NMR Spectrum of 8b in Chloroform-*D*

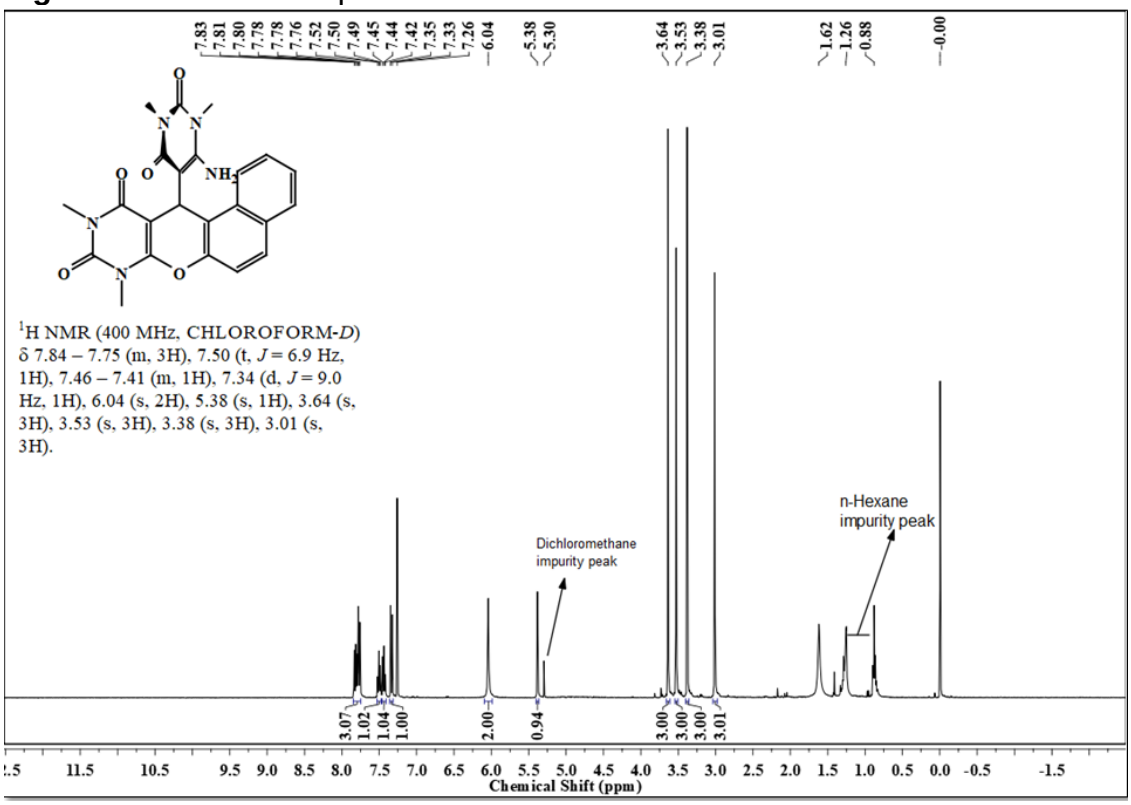
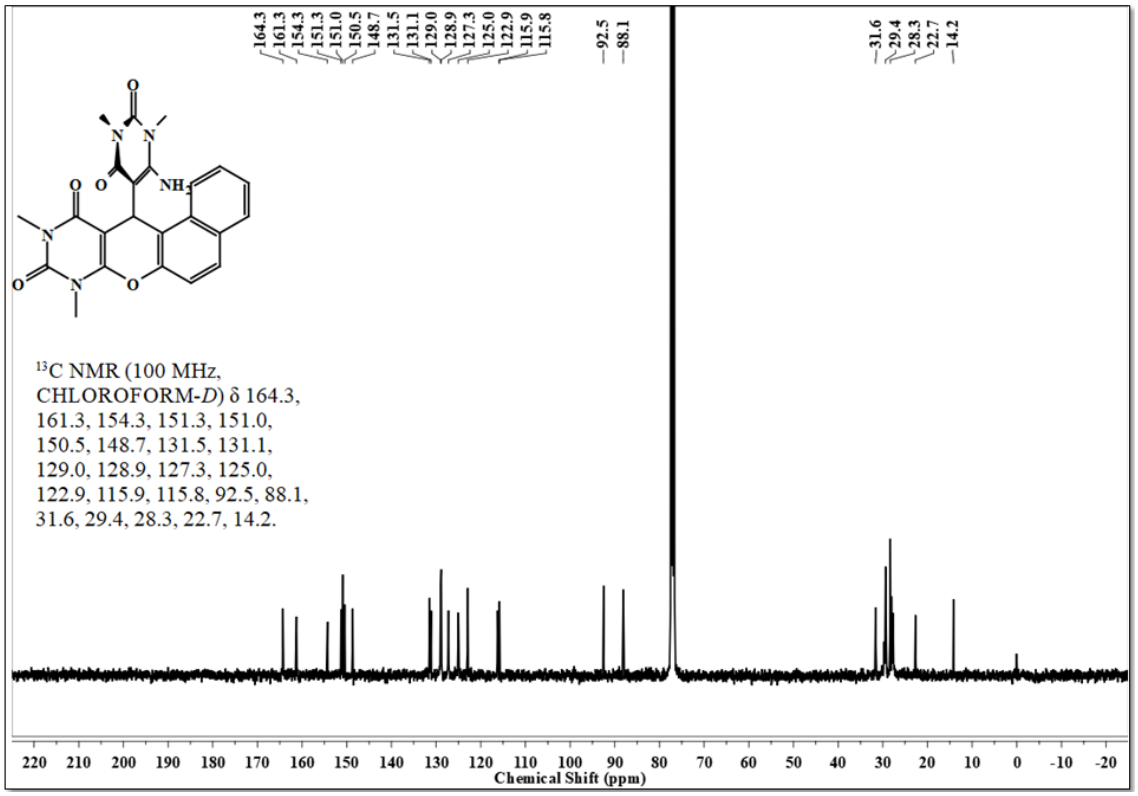


Figure 3.2.10 ^{13}C NMR Spectrum of 8b in Chloroform-*D*



REFERENCES

[1] Khalaj, M., Mousavi-Safavi, S. M., Farahani, N., and Lipkowski, J. MgO nanopowders catalyzed synthesis of pyrano[4,3-*d*]thiazolo[3,2-*a*]pyrimidine derivatives. *Applied Organometallic Chemistry*, 34(10):e5865, 2020.

[2] Khalaj, M. Preparation of benzo[4,5]thiazolo[3,2-*a*]chromeno[4,3-*d*]pyrimidin-6-one derivatives using MgO-$MgAl_2O_4$ composite nano-powder. *Arabian Journal of Chemistry*, 13(8):6403-6411, 2020.

[3] Ziyaadini, M., Roudbaraki, S. J., and Ghashang, M. Ionic-liquid Promoted Multi-component preparation of Pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines under solvent-free conditions. *Organic Preparations and Procedures International*, 52(4):311-318, 2020.

[4] Shafighi, S., Mohammad Shafiee, M. R., and Ghashang, M. MgO-CeO_2 nanocomposite: efficient catalyst for the preparation of 2-*a*minothiophenes and thieno[2,3-*d*]pyrimidin-4(3*H*)-one derivatives. *Journal of Sulfur Chemistry*, 39(4):402-413, 2018.

[5] Abaszadeh, M., Roudbaraki, S. J., and Ghashang, M. Effect of liquid glass composition on the catalytic preparation of pyrano[2,3-*d*]pyrimidine derivatives. *Organic Preparations and Procedures International*, 51(3):255-269, 2019.

[6] Roudbaraki, S. J., Ziyaadini, M., and Ghashang, M. multi-component preparation of Pyrazolo[3,4-*d*]thiazolo[3,2-*a*]pyrimidines using solvent-free and HSBM techniques. *Letters in Organic Chemistry*, 17(7):512-516, 2020.

[7] Jain, S., Paliwal, P. K., Babu, G. N., and Bhatewara, A. DABCO promoted one-pot synthesis of dihydropyranochromene and pyrano[2,3-*d*]pyrimidine derivatives and their biological activities. *Journal of Saudi Chemical Society*, 18(5):535-540, 2014.

[8] Xie, H., Lin, X., Zhang, Y., Tan, F., Chi, B., Peng, Z., and An, D. Design, synthesis and biological evaluation of ring-fused pyrazoloamino pyridine/pyrimidine derivatives as potential FAK inhibitors. *Bioorganic and Medicinal Chemistry Letters*, 30(21):127459-127464, 2020.

[9] Radwan, E. M., Elsayed, E. H., El-Moneim, M. A., and Moustafa, A. M. Y. design, synthesis, and anti-breast cancer activity of some hybrid molecules containing coumarin moiety. *Russian Journal of Bioorganic Chemistry*, 47: 149-157, 2021.

[10] He, Z. X., Zhao, T. Q., Gong, Y. P., Zhang, X., Ma, L. Y., and Liu, H. M. Pyrimidine: A promising scaffold for optimization to develop the inhibitors of ABC transporters. *European Journal of Medicinal Chemistry*, 200:112458-112468, 2020.

[11] Awad, L. F., Teleb, M., Ibrahim, N. A., Abu-Serie, M. M., and Abd Al Moaty, M. N. Structure-based design and optimization of pyrimidine-*a*nd 1,2,4-triazolo[4,3-*a*]pyrimidine-based matrix metalloproteinase-10/13 inhibitors via Dimroth rearrangement towards targeted polypharmacology. *Bioorganic Chemistry*, 96:103616-103625, 2020.

[12] Xiong, J., Wang, J., Hu, G., Zhao, W., and Li, J. Design, synthesis and biological evaluation of novel, orally bioavailable pyrimidine-fused heterocycles as influenza PB_2 inhibitors. *European Journal of Medicinal Chemistry*, 162:249-265: 2019.

[13] Oukoloff, K., Nzou, G., Varricchio, C., Lucero, B., Alle, T., Kovalevich, J., and Ballatore, C. Evaluation of the structure–activity relationship of microtubule-targeting 1,2,4-Triazolo[1,5-*a*]pyrimidines identifies new candidates for neurodegenerative tauopathies. *Journal of Medicinal Chemistry*, 64(2):1073-1102, 2021.

[14] Namasivayam, V., Stefan, K., Pahnke, J., and Stefan, S. M. Binding mode analysis of ABCA7 for the prediction of novel Alzheimer's disease therapeutics. *Computational and Structural Biotechnology Journal*, 19:6490-6504, 2021.

[15] Curini, M., Cravotto, G., Epifano, F., and Giannone, G. Chemistry and biological activity of natural and synthetic prenyloxycoumarins. *Current Medicinal Chemistry*, 13(2):199-222, 2006.

[16] Lacy, A., and O'Kennedy, R. Studies on coumarins and coumarin-related compounds to determine their therapeutic role in the treatment of cancer. *Current Pharmaceutical Design*, 10(30):3797-3811, 2004.

[17] Borges, F., Roleira, F., Milhazes, N., Santana, L., and Uriarte, E. Simple coumarins and analogues in medicinal chemistry: occurrence, synthesis and biological activity. *Current Medicinal Chemistry*, 12(8):887-916, 2005.

[18] Tangmouo, J. G., Meli, A. L., Komguem, J., Kuete, V., Ngounou, F. N., Lontsi, D., and Sondengam, B. L. Crassiflorone, a new naphthoquinone from *Diospyros crassiflora* (Hien). *Tetrahedron Letters*, 47(18):3067-3070, 2006.

[19] Kitamura, R. O. S., Romoff, P., Young, M. C. M., Kato, M. J., and Lago, J. H. G. Chromenes from *Peperomia serpens* (Sw.) Loudon (Piperaceae). *Phytochemistry*, 67(21):2398-2402, 2006.

[20] Abdelrazek, F. M., Metz, P., Kataeva, O., Jäger, A., and El-Mahrouky, S. F. Synthesis and molluscicidal activity of new chromene and pyrano[2,3-*c*]pyrazole derivatives. *Archiv der Pharmazie: An International Journal Pharmaceutical and Medicinal Chemistry*, 340(10):543-548, 2007.

[21] Singh, K., Singh, J., and Singh, H. A synthetic entry into fused pyran derivatives through carbon transfer reactions of 1,3-oxazinanes and oxazolidines with carbon nucleophiles. *Tetrahedron*, 52(45):14273-14280, 1996.

[22] Andrianasolo, E. H., Haramaty, L., Rosario-Passapera, R., Vetriani, C., Falkowski, P., White, E., and Lutz, R. Ammonificins C and D, hydroxyethylamine chromene derivatives from a cultured marine hydrothermal vent bacterium, *Thermovibrio ammonificans*. *Marine Drugs*, 10(10):2300-2311, 2012.

[23] Curini, M., Cravotto, G., Epifano, F., and Giannone, G. Chemistry and biological activity of natural and synthetic prenyloxycoumarins. *Current Medicinal Chemistry*, 13(2):199-222, 2006.

[24] Cingolani, G., Gualtieri, F., and Pigini, M. Researches in the field of antiviral compounds. Mannich bases of 3-hydroxycoumarin. *Journal of Medicinal Chemistry*, 12(3):531-532, 1969.

[25] Smith, P. W., Sollis, S. L., Howes, P. D., Cherry, P. C., Starkey, I. D., Cobley, K. N., and Beresford, A. Dihydropyrancarboxamides related to zanamivir: A new series of inhibitors of influenza virus sialidases. 1. Discovery, synthesis, biological activity, and structure− activity relationships of 4-guanidino- and 4-*a*mino-4*H*-pyran-6-carboxamides. *Journal of Medicinal Chemistry*, 41(6):787-797, 1998.

[26] *de* Andrade-Neto, V. F., Goulart, M. O., *da* Silva Filho, J. F., *da* Silva, M. J., Maria *do* Carmo, F. R., Pinto, A. V., and Krettli, A. U. Antimalarial activity of phenazines from lapachol, β-lapachone and its derivatives against *Plasmodium falciparum in vitro* and *Plasmodium berghei in vivo*. *Bioorganic and Medicinal Chemistry Letters*, 14(5):1145-1149, 2004.

[27] Anderson, D. R., Hegde, S., Reinhard, E., Gomez, L., Vernier, W. F., Lee, L., and Sambandam, P. A. Snider and Masih, L. *Bioorganic and Medicinal Chemistry Letters*, 15:1587-1593, 2005.

[28] Ough, M., Lewis, A., Bey, E. A., Gao, J., Ritchie, J. M., Bornmann, W., and Cullen, J. J. Efficacy of beta-lapachone in pancreatic cancer treatment: exploiting the novel, therapeutic target NQO1. *Cancer Biology and Therapy*, 4(1):102-109, 2005.

[29] Cheng, J. F., Ishikawa, A., Ono, Y., Arrhenius, T., and Nadzan, A. Novel chromene derivatives as TNF-α inhibitors. *Bioorganic and Medicinal Chemistry Letters*, 13(21):3647-3650, 2003.

[30] Brahmachari, G. *Handbook of Pharmaceutical Natural Products* (Vol. 1, p. 323). Weinheim:Wiley-VCH, New York, 2010.

[31] Khan, A. T., Lal, M., Ali, S., and Khan, M. M. One-pot three-component reaction for the synthesis of pyran annulated heterocyclic compounds using DMAP as a catalyst. *Tetrahedron Letters*, 52(41):5327-5332, 2011.

[32] Elagamey, A. G. A., El-Taweel, F. M. A. A., Khodeir, M. N. M., and Elnagdi, M. H. Nitriles in heterocyclic synthesis. The reaction of polyhydric naphthalenes, 4-methylcoumarin-3-carbonitrile, and alkylidenemalononitrile with methylenemalononitrile. *Bulletin of the Chemical Society of Japan*, 66(2):464-468, 1993.

[33] Rai, U. S., Isloor, A. M., Vijesh, A. M., Prabhu, N., Isloor, S., Thiageeswaran, M., and Fun, H. K. Novel chromeno[2,3-*b*]-pyrimidine derivatives as potential anti-microbial agents. *European Journal of Medicinal Chemistry*, 45(6):2695-2699, 2010.

[34] Mobinikhaledi, A., Foroughifar, N., Mosleh, T., and Hamta, A. Synthesis of some novel chromenopyrimidine derivatives and evaluation of their biological activities. *Iranian Journal of Pharmaceutical Research: IJPR*, 13(3):873-882, 2014.

[35] Suresh, L., Kumar, P. S. V., and Chandramouli, G. V. P. An efficient one-pot synthesis, characterization and antibacterial activity of novel chromeno-pyrimidine derivatives. *Journal of Molecular Structure*, 1134:51-58, 2017.

[36] Bhosle, M. R., Wahul, D. B., Bondle, G. M., Sarkate, A., and Tiwari, S. V. An efficient multicomponent synthesis and in vitro anticancer activity of dihydropyranochromene and chromenopyrimidine-2,5-diones. *Synthetic Communications*, 48(16):2046-2060, 2018.

[37] Malviya, J., and Singh, R. K. P. One-pot three-component synthesis of chromeno[2,3-*d*]pyrimidine derivatives: Novel, simple, and efficient electrochemical approach. *Journal of Heterocyclic Chemistry*, 57(1):39-49, 2020.

[38] Biot, C., and Chibale, K. Novel approaches to antimalarial drug discovery. *Infectious Disorders-Drug Targets,* 6(2):173-204, 2006.

[39] Viegas-Junior, C., Danuello, A., *da* Silva Bolzani, V., Barreiro, E. J., and Fraga, C. A. M. Molecular hybridization: a useful tool in the design of new drug prototypes. *Current Medicinal Chemistry*, 14(17):1829-1852, 2007.

[40] Dömling, A. Recent advances in isocyanide-based multicomponent chemistry. *Current Opinion in Chemical Biology*, 6(3):306-313, 2002.

[41] Schreiber, S. L. Target-oriented and diversity-oriented organic synthesis in drug discovery. *Science*, 287(5460):1964-1969, 2000.

[42] Xiabing, M., Ablajan, K., Obul, M., Seydimemet, M., Ruzi, R., and Wenbo, L. Facial one-pot, three-component synthesis of thiazole compounds by the

reactions of aldehyde/ketone, thiosemicarbazide and chlorinated carboxylic ester derivatives. *Tetrahedron*, 72(18):2349-2353, 2016.

[43] Manjappa, K. B., Peng, Y. T., Jhang, W. F., and Yang, D. Y. Microwave-promoted, catalyst-free, multi-component reaction of proline, aldehyde, 1,3-diketone: One pot synthesis of pyrrolizidines and pyrrolizinones. *Tetrahedron*, 72(6):853-861, 2016.

[44] Zhang, X., Wang, Z., Xu, K., Feng, Y., Zhao, W., Xu, X. and Yi, W. HOTf-catalysed sustainable one-pot synthesis of benzene and pyridine derivatives under solvent-free conditions. *Green Chemistry*, 18(8):2313-2316, 2016.

[45] Brahmachari, G. and Banerjee, B. Catalyst-free organic synthesis at room temperature in aqueous and non-aqueous media: an emerging field of green chemistry practice and sustainability. *Current Green Chemistry*, 2(3):274-305, 2015.

[46] Verma, A. K., Kotla, S. K. R., Choudhary, D., Patel, M., and Tiwari, R. K. (2013). Silver-catalyzed tandem synthesis of naphthyridines and thienopyridines via three-component reaction. *The Journal of Organic Chemistry*, 78(9):4386-4401, 2013.

[47] Srinivas, V., and Koketsu, M. Synthesis of indole-2-, 3-, or 5-substituted propargylamines via gold (III)-catalyzed three component reaction of aldehyde, alkyne, and amine in aqueous medium. *Tetrahedron*, 69(37):8025-8033, 2013.

[48] Brahmachari, G. and Nayek, N. Catalyst-free one-pot three-component synthesis of diversely substituted 5-aryl-2-oxo-/thioxo-2,3-dihydro-1*H*-benzo[6,7]chromeno[2,3-*d*]pyrimidine-4,6,11(5*H*)-triones under ambient conditions. *ACS Omega*, 2(8):5025-5035, 2017.

[49] Khurana, J. M., Chaudhary, A., Lumb, A., and Nand, B. An expedient four-component domino protocol for the synthesis of novel benzo[*a*]phenazine annulated heterocycles and their photophysical studies. *Green Chemistry*, 14(8):2321-2327, 2012.

[50] Singh, M. S. and Chowdhury, S. Recent developments in solvent-free multicomponent reactions: a perfect synergy for eco-compatible organic synthesis. *RSC Advances*, 2(11):4547-4592, 2012.

[51] D. J. Brown. *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky and C. W. Rees, Pergamon Press, Oxford, UK, 14, 1984.

[52] R. C. Elderfield. *Heterocyclic Compounds*, John Wiley and Sons, New York, NY, USA, 6, 1957.

[53] Zeng, L. Y., Lv, M. F., and Cai, C. Iodine catalyzed synthesis of the chromene derivatives in one-pot. *Chinese Chemical Letters*, 23(12):1347–1351, 2012

[54] Patil, J. D., Korade, S. N., and Pore, D. M. 1,1′-Sulfinyldipyridinium bis (hydrogen sulfate) ionic liquid: synthesis and application in the temperature-influenced synthesis of novel pyranopyrimidinediones and pyranopyrimidinetriones. *RSC Advances*, 4(92):50449-50455, 2014.

[55] Elinson, M. N., Nasybullin, R. F., Sokolova, O. O., Zaimovskaya, T. A., and Egorov, M. P. Non-catalytic multicomponent rapid and efficient approach to 10-(2,4,6-trioxohexahydropyrimidin-5-yl)-3,3-dimethyl-2,3,4,9-tetrahydro-1*H*-xanthen-1-ones from salicylaldehydes, dimedone, and barbituric acids. *Monatshefte für Chemie-Chemical Monthly*, 146:1689-1694, 2015.

[56] Tajbakhsh, M., Heidary, M., Hosseinzadeh, R., and Amiri, M. A. $FeCl_3 \cdot 6H_2O$ as a green and readily available catalyst for the synthesis of 1-oxo-hexahydroxanthenes by the condensation of salicylaldehydes with 1,3-diketones in aqueous media. *Tetrahedron Letters*, 57(1): 141-145, 2016.

[57] Lohar, T., Mane, A., Kamat, S., Kumbhar, A., and Salunkhe, R. Trifluoroethanol and liquid-assisted grinding method: a green catalytic access for multicomponent synthesis. *Research on Chemical Intermediates*, 44:1919-1933, 2018.

[58] Dige, N. C., Mahajan, P. G., Dhokale, R. K., Chinchkar, S. M., Patil, M. V., and Pore, D. M. Novel Route for the Synthesis of 5-(4-Hydroxy-2-oxo-2*H*-chromen-3-yl)-1,3-dimethyl-1*H*-chromeno[2,3-*d*]pyrimidine-2,4(*3H*,5*H*)-

diones. *Organic Preparations and Procedures International*, 51(6):553-565, 2019.

[59] Korade, S.N., Patil, J.D., Gaikwad, D.S., Sonawane, S.A., Vibhute, S.P., Dige, N.C., Mhaldar, P.M. and Pore, D.M., Synthesis and biological activities of novel aryldiazo substituted heterocycles. *Organic Preparations and Procedures International*, 52(2):147-165, 2020.

[60] Ram, S., and Sharma, P. K. (2023). A Review on Molecular Iodine Catalyzed/Mediated Multicomponent Reactions. *Asian Journal of Organic Chemistry*, 12(1):e202200616-635, 2023.