CHAPTER 2

On-water multicomponent synthesis of 5-aryl-pyrano[2,3-*d*:6,5-*d*′]dipyrimidinetetraones

INTRODUCTION

Uracil is one of the nucleobases which is found in abundance in natural products and because of its prodigious biological properties, it has caught the interest of many [1,2]. Their laudable pharmaceutical properties include antimicrobial [3], analgesic [4], anti-inflammatory [5], anti-cancer [6], and acaricidal [7] effects. 6-aminouracil and its derivatives happen to be interesting functionalities of the uracil family as it bears dual nature of an electrophile and a nucleophile [8]. Therefore, it appears as a precursor to several biologically active relevant heterocyclic scaffolds such as pyrrolo-, pyrido-, pyrimido, and pyrano-pyrimidines etc [9-14].

Pyranopyrimidines are a class of fused bicyclic uracil moieties which constitute the matrices of many well-documented biologically active agents showing analgesic [15], antifungal [16], antitumor [17], antihypertensive [18], antimalarial 19], antiallergic [20], anti-inflammatory [21], cardiotonic [22] and hepatoprotective [23] properties. Pyranopyrimidines fused with coumarin ring are used as fungicides [24] and herbicides [25]. Naphthopyranopyrimidines are biologically interesting compounds inherent with antimicrobial properties (entry **a** of **Figure 2.1**) [26]. Chromenopyrimidones have been tested to have inhibitory effects on α-amylase and α- glucosidase, implying up on the pleiotropic effects against diabetes complications (entry **b** of **Figure 2.1**) [27]. Neuropeptide S receptor (entry **c** of **Figure 2.1**) previously known as GPR154, is highly expressed in brain areas and have been implicated in modulation of arousal, stress and anxiety, thereby being a suitable candidate for the treatment of sleep and anxiety

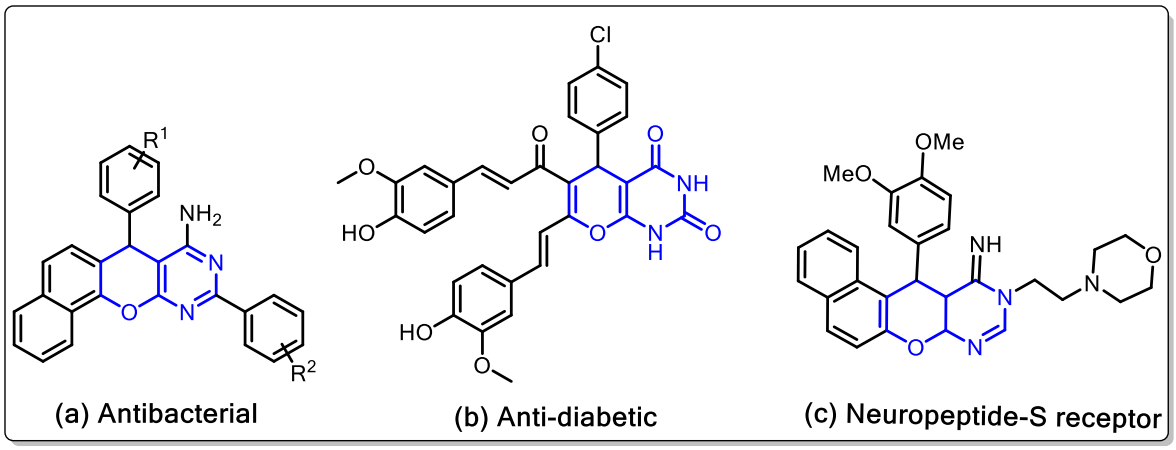


Figure 2.1 Bioactive pyranopyrimidine molecules

disorders [28]. Hence, efforts are being made to synthesize this skeleton despite the synthetic challenges that comes on the way. A subclass to this skeleton is the pyranodipyrimidines, the least investigated among all, yet holds a special point of note among the annulated pyrimidine molecules. It was the very first scaffold to appear as HIV-I integrase enzyme inhibitor, was commercialised by the name of V-165 (**Figure 2.2**) and used for the treatment of the deadly human immunodeficiency virus (HIV) [29]. The synthesis route was simple and involved condensation of *bis*-barbiturates.

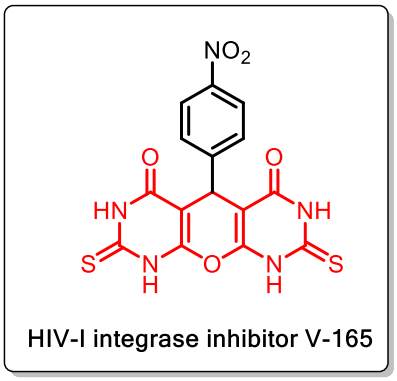


Figure 2.2: Anti-HIV drug

The tricyclic system plays an important role in various other biological activities, with potency ranging from being antibacterial, immunomodulating, and antitumor

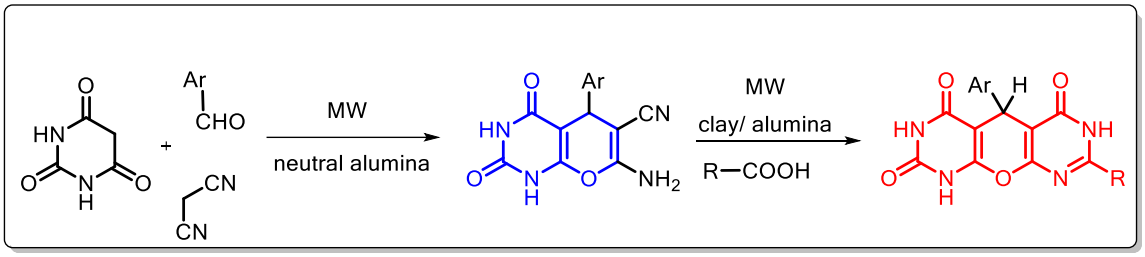
[30] to antiretroviral drugs [31]. It was an important point to note from the available reports that N- alkylated products showed enhanced bioactivity due to the increase in solubility in common organic solvent which indicates high lipophilicity and as a result of which facilitates membrane transport and strengthens functional activity [32]. Despite being a potent medicinal scaffold it is disheartening to state that the synthesis of pyranodipyrimidones has been limited to acid catalysed methodologies resulting in either symmetrical pyranodipyrimido-tetraones or other varied tricyclic rings. Many a times the result was chromeno derivatives and other times it was pyranopyrimido-diones. But, when our interest lies in the tetraones rather than diones, the formulation of new strategy is demanded for.

For a long time organic synthesis has been a matter of application of classical methodologies, where people relied on altering either reactants or reaction conditions to achieve the desired products. This however, many a times, led to compromising the parameters which now forms the basis of green chemistry. The continual upsurge in facile, convenient and non-polluting synthetic procedures urges chemists to increase their search for newer tools. One approach that has effectively faced this challenge and also holds the answers to many stubbles, is the environmentally benign multicomponent approach. They have gained popularity in the recent years owing to their flexibility, convergence and efficiency. They provide efficient access to complex molecules and an ideal platform for rapid generation of both complexity and diversity in a collection of compounds with predefined functionality.

Domino reaction, an important subclass or Multicomponent reactions (MCRs) is a one pot process in which two or more bond transformations take place one after another to form a single product, that incorporates essentially most or all atoms in the starting materials. Such reactions bear all the characteristics of a MCR and are a shade better with respect to the sequence of addition of reactants. Here all the reactants are dumped in to one pot and the reaction proceeds through the formation of one bond after another without a demand for any interfering activity, such as addition of any more reactant. But, this process comes with its own limitations and not all multicomponent reactions can be carried out in domino fashion. The limitations may arise due to the presence of competing functionalities in the participating components in the reaction and because of which a sequential addition of reactants is preferred over domino.

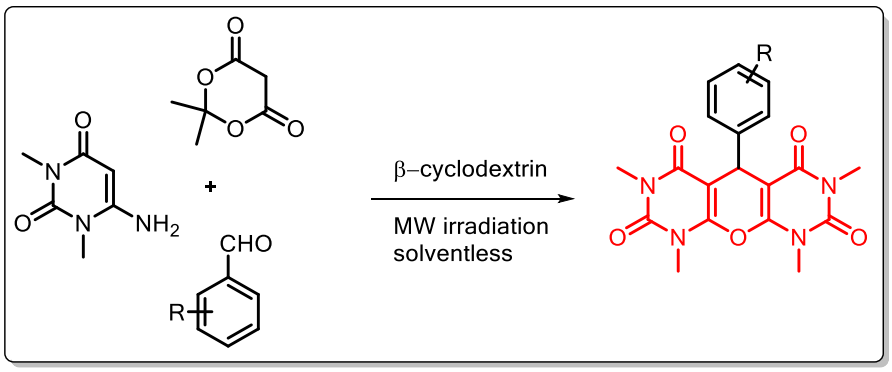
Barbituric acid and Uracil are the two compounds having very similar skeleton i.e.; pyrimidine. The latter is the most abundant ribonucleic acid constituting nitrogenous base, found even outside the cell. The biological potency of these skeletal molecules instigated our search for the challenges in pyrimidine chemistry. As stated earlier, pyranodipyrimidones are the least explored sections of annulated pyrimidines, therefore, it caught our interests. Reports on the acid catalysed synthesis of symmetrical pyranodipyrimidones, even tetraones are available. A multicomponent reaction was reported by Kidwai *et al.* in 2007 [33] where a microwave assisted route towards the synthesis of pyranopyrimidones was reported. It was a two-step reaction and as stated by them, it lacked the possibilities of domino strategy. The Biginelli product formed by the condensation

of malononitrile, barbituric acid and aromatic aldehyde was reacted with an aromatic carboxylic acid under microwave irradiation in the presence of clay/alumina to result in pyranodipyrimido-triones (**Scheme 2.1**). Although the reaction time was less and yield obtained was very good but conducting a two-step reaction has its own demerits, especially with losses that may be incurred during the isolation of products in each step.



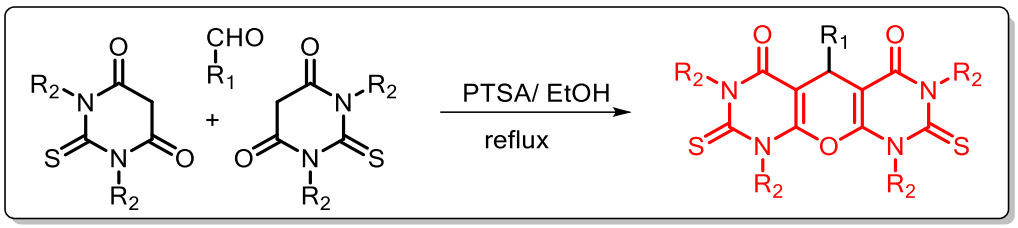
Scheme 2.1 Two-step synthesis of unsymmetrical pyranodipyrimidones (Kidwai *et al.*)

Avvadukkam *et al.* in 2021 reported a three component synthesis of pyrano[2,3-*d*:6,5-*d*']dipyrimidines from 6-amino-1,3-dimethyluracil, Meldrum's acid and aromatic aldehyde under MW irradiation and in solventless condition (**Scheme 2.2**) [1]. The reaction was catalysed by β-cyclodextrin and the products formed were in good yields.



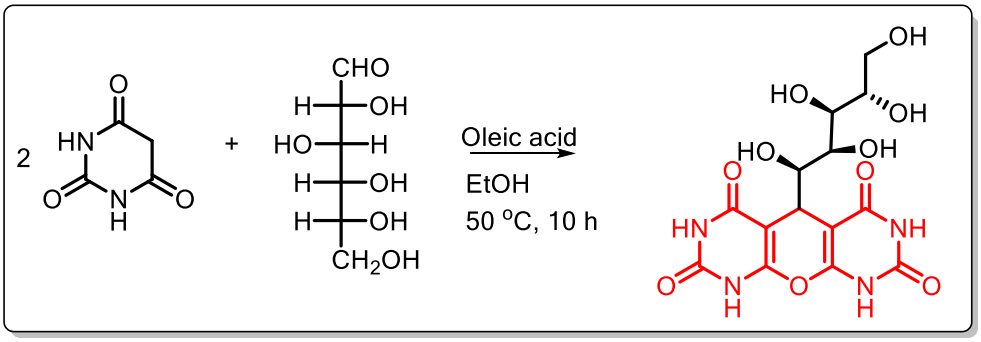
Scheme 2.2 β-cyclodextrin catalysed three component reaction for the synthesis of pyrano[2,3-*d*:6,5-*d*']dipyrimidines under MW irradiations (Avvadukkam *et al.*)

Mahmoodi *et al.* in 2016 [34] reported *p*-Toluenesulfonic acid catalysed one pot synthesis of 2,8-dithioxopyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(1*H*)-dione. The route was simple and the stated compound was formed by condensing *bis*thiobarbiturates (**Scheme 2.3**). The reaction was stated to be multicomponent tandem and yields were excellent.



Scheme 2.3 *p*-Toluenesulfonic acid catalysed one pot synthesis of 2,8-dithioxopyrano[2,3-*d*:6,5-*d*′]dipyrimidine-4,6(1*H*)-dione (Mahmoodi *et al.*)

Similar reports could be found in the past where people have altered the acid catalyst and synthesised very similar classes of compounds. Ganesan *et al.* in 2016 [26] reported about oleic acid catalysis in to designing chromenopyranopyrimidines, pyrazolopyranopyrimidones and symmetrical pyranodipyrimidones. The reactions were carried out in aqueous conditions at 50 ^{o}C and even found success with aliphatic aldehydes (**Scheme 2.4**). However, the reaction suffered from prolonged duration to achieve completion.

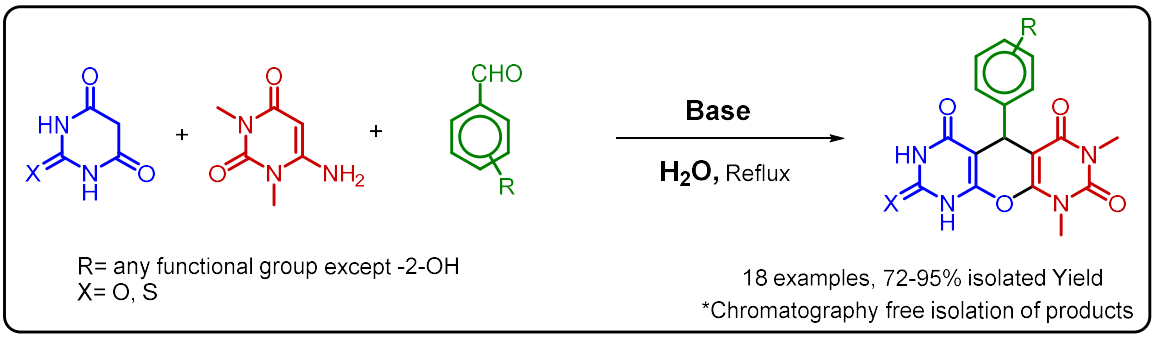


Scheme 2.4 Naturally available oleic acid catalysed synthesis of symmetrical pyranodipyrimidones (Ganesan *et al.*)

We learnt from the reports that the synthesis of unsymmetrical pyranodipyrimido-tetraones can be done *via* domino fashion. Designing a route for the synthesis of unsymmetrical pyranodipyrimido-tetraones from barbituric acid, aromatic aldehyde and 6-aminouracils is the prime focus of this work. The principles of green chemistry were kept in mind while designing the routes and are accomplished on water. In the following two sections the development of two protocols, of which the first will be a base mediated route for the synthesis of pyranodipyrimidines (**section 2.1**), is discussed. The novelty of the route lies in the fact that unsymmetrical pyranopyrimidines will be synthesised along with symmetrical analogues. Later, a modification will be made to the reagents and a catalytic approach is shown in the next section (**section 2.2**).

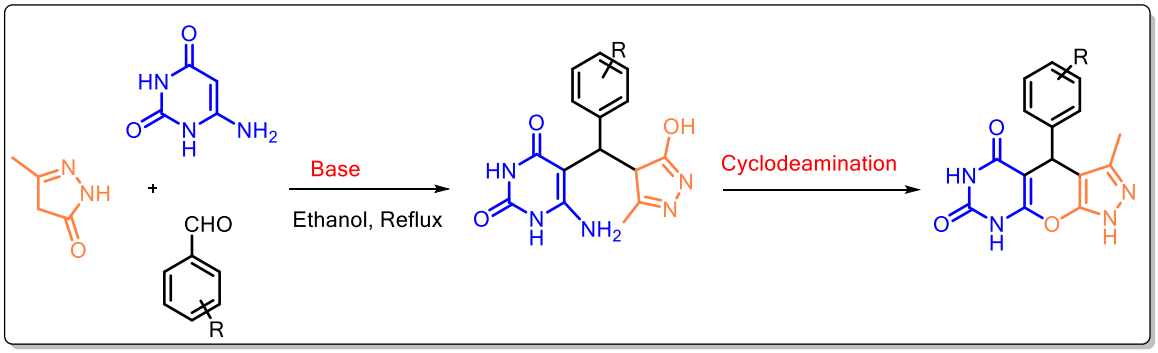
SECTION 2.1

Base mediated synthesis of unsymmetrical 5-aryl-pyrano[2,3-*d*:6,5-*d*']dipyrimidinetetraones



2.1.1 INTRODUCTION

Pyrano-dipyrimidines hold a huge prospect to be explored as a potential biologically active candidate and therefore, its synthesis has given a platform to several researchers to develop newer methodologies for its synthesis and modifications. We have already visited the different ways it has been synthesised using various acid catalysts/media. But the question related to its formation under basic conditions intrigued us to search for possibilities. Also, we were more interested in designing unsymmetrical pyranodipyrimidines than the symmetrical counterparts. While searching for literature to support our endeavour, we came across a report by Panda *et al.* published in 2016 [35], where it was shown that pyridopyranopyrimidines could be synthesised *via* a base driven domino approach using pyrazolone, aromatic aldehyde and 6-aminouracil. The reaction proceeded *via* Knoevenagel condensation- Michael addition- cyclodeamination sequential route (**Scheme 2.1.1**).



Scheme 2.1.1 Base driven domino synthesis of pyridopyranopyrimidones *via* cyclodeamination (Panda *et al.*)

The report was exclusively on medicinal properties of the class of compounds and the plausible mechanism was not provided in detail. Also, no comments were

made regarding the cyclodeamination step. This was essential because prior to this step a triarylmethane intermediate, bearing two labile groups namely, –OH and $–NH_2$ is formed. In the presence of acid, cyclodehydration occurs while, as stated in this research paper, in the presence of a base cyclodeamination occurs. And to our relief, we came across the report of Nandi *et al.* [25] wherein the synthesis of naphthopyranopyrimidine was reported and it was discussed that in the presence of both the nucleophilic groups; certain parameters, such as the presence of base, could result in cyclodeamination and hence result in the formation of the pyrano ring instead of the pyrido ring. These two reports gave a foundation to our hypothesis that two different pyrimidine sources and an aldehyde could be used to form the pyranodipyrimidine ring, in the presence of a base *via* the cyclodeamination step. Also, we had the motive to make the reaction greener by using water as the solvent and carrying out the reaction in domino fashion.

2.1.2 RESULTS AND DISCUSSION

Following the procedure reported by Panda *et al.* towards the synthesis of pyrazolopyranopyrimidones, the reaction was initiated with a stirred aqueous solution of Barbituric acid (1 mmol) and *N,N′*-dimethylaminobenzaldehyde (1 mmol) at room temperature. No base was added at this stage. The reaction resulted in the precipitation of an orange colour solid product, which after isolation and characterisation with the help of ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectroscopy, was found to be the Knoevenagel condensation product, i.e. the arylidene barbiturate. Following this, the reaction vessel with the

obtained precipitate was charged with 2.0 mmol of Potassium Carbonate and 1 mmol of 6-amino-1,3-dimethyluracil. Stirring at room temperature was continued and the reaction was monitored by TLC for 24 h. Upon addition of the base, the heterogeneous orange reaction mixture turned to a clear deep red solution and at the end of the mentioned time, some amount of yellow precipitate was observed to be formed, although a majority of the reaction mixture was still of deep red colouration. Upon monitoring *via* TLC, it was found that the arylidene barbiturate and 6-aminouracil was left unreacted and a new product was formed. To check the improvement of the reaction upon elevation of the reaction temperature, it was continued under reflux. As the reaction progressed, the deep red colouration of the reaction mixture started to disappear and a pale yellow precipitate separated out of the solution. At the end of 3 hours, the reaction was stopped and the reaction mixture was examined with the help of TLC. It was observed that both, the arylidene barbiturate and 6-amino-1,3-dimethyluracil were consumed and the previously obtained new spot was the prominent entity present. The precipitate was collected by filtration and washed multiple times with ethanol, followed by drying under vacuum. Then came the next question that whether it was the cyclised product and if yes, whether it was the pyrano- or the pyrido-derivative. The dried product (**4a**) was analysed with the aid of ^{1}H, ^{13}C NMR and mass spectrometry and it was found that the desired pyran ring containing product was formed. The characteristic –CH proton peak of the pyran ring which showed resonance as a singlet at δ 4.58 ppm was present. In ^{13}C NMR, the –CH carbon showed resonance at δ 51.3 ppm. The mass spectrum showed a molecular ion peak at m/z 383.1397 $(M+H)^{+}$, which correlated with its molecular

formula: $C_{19}H_{19}N_5O_5$. This first attempt helped us draw a few conclusions. They are as follows:

1. An unsymmetrical pyranodipyrimidine product was formed.
2. The product was a result of domino Michael addition of the 6-amino-1,3-dimethyluracil to the Knoevenagel product (5-arylidene barbiturate) followed by base mediated deamination and cyclisation.
3. The formation of the new product could be monitored by the change in colour of the reaction mixture. This point was thoroughly established while the generalisation of the scheme was later carried out.
4. Temperature is an essential factor for the reaction.
5. Sequence of addition of reactants could be checked.

To check the effect of the sequence of addition of reactants, 6-aminouracil was added to the aldehyde first, stirred for a while and then barbituric acid with the base was introduced. It was observed that a mixture of products was formed along with the desired compound and prominent among them was *bis* uracil. This was not the end of the study. We aimed at a domino approach and so we tested for the feasibility and selectivity of the reaction. The three reactants were introduced at the same time in aqueous medium, stirred under room temperature until the formation of the Knoevenagel condensation product was confirmed by the formation of the orange precipitate and then potassium carbonate was introduced to the reaction mixture. The reaction was then put to reflux and to our surprise the transformations occurred at a much faster rate. The desired product was formed within 1.5 hours. The side products, which were not incorrect to

expect, were not present even in traces. This helped to draw a conclusion that barbituric acid reacted immediately with the aldehyde to form the Knoevenagel condensation adduct and 6-amino-1,3-dimethyluracil did not participate in the reaction until the introduction of the base. Also, the nucleophilicity of barbituric acid could be said to be more than 6-amino-1,3-dimethyluracil. Following the establishment of the procedure for the synthesis of the desired unsymmetrical pyranodipyrimidine product, i.e. 1,3-dialkyl-5-aryl-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8-tetraone optimisation of the reaction scheme in terms of the nature of base, solvent and temperature, was carried out.

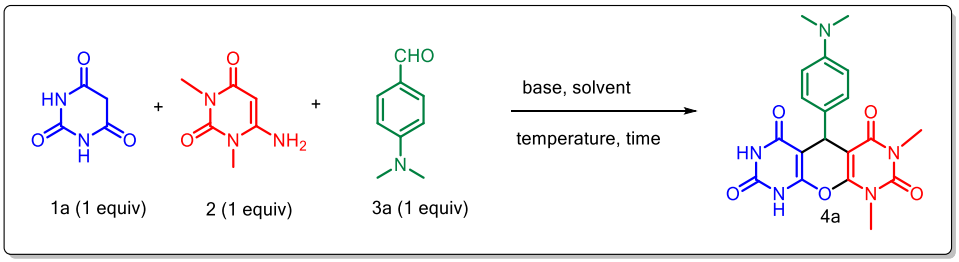
Optimisation of the reaction system

The reaction between barbituric acid, 4-*N,N′*-dimethylaminobenzaldehyde and 6-amino-1,3-dimethyluracil was taken as the model reaction and the reaction conditions were optimised in terms of the base used, reaction time, temperature and solvent. The reasons for choosing these substrates as the model are availability of the compounds and also ease of observation. There is a distinct change in colour at each step and the final product obtained is in high yields. Reactions were carried out in polar protic (EtOH, H_2O, H_2O:EtOH (1:1)), polar aprotic: dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), acetonitrile (CH_3CN), 1,2-dichloroethane (DCE) and non- polar solvent (toluene) for finding the suitable solvent. The amount of solvent used was 5mL. The reaction was carried out at 80 ^oC with 1.5 equivalents of K_2CO_3. It was found that the reaction proceeded equally well in EtOH, DMSO, H_2O and H_2O:EtOH (1:1). The conversion, as evident from the TLC was comparable but when it came to isolate

the product, problems began. It was only in case of water that the product separated out as solid, whereas in all other solvents it remained in solution. The prospect of using any other immiscible organic solvent to isolate the product resulted in loss of isolated yield %. Therefore, we stuck to water as the solvent of our choice. No results obtained with DCE and Toluene.

We know that mild bases are usually preferred in reactions so as to avoid unnecessary by products. Thus the study was initiated with potassium carbonate. The variations in the amount of base used is summarised in the optimisation table (**table 2.1.1**). The reaction proceeded well with 1.5 equivalents of the base and resulted in the optimum yield. Sodium hydroxide and Caesium Carbonate also resulted in comparable yields but they were not used for their strong nature. Organic base such as triethyl amine gave lower yields. It was also seen that in the absence of the base only the Knoevenagel product was formed and the reaction did not proceed further.

Table 2.1.1 Optimisation of the reaction



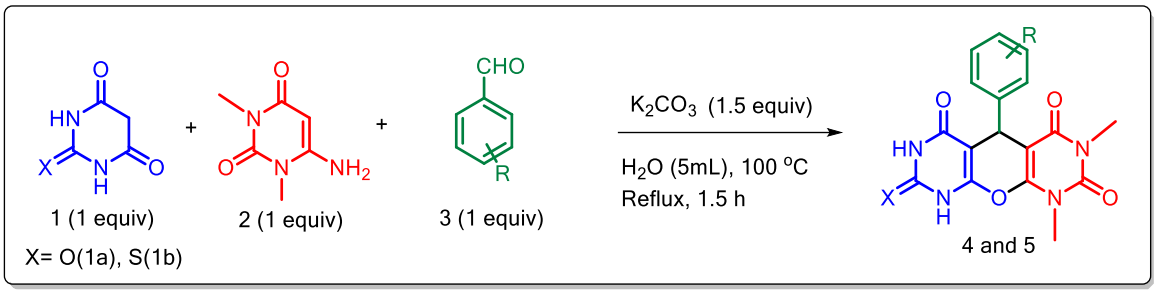
Entry	Base (mmol)	Solvent (5 mL)	Temperature (˚C)	Time (h)	Isolated Yield %
1	K_2CO_3 (2.5)	H_2O	100	2	95
2	K_2CO_3 (2.0)	H_2O	100	2	95
3	K_2CO_3 (1.5)	H_2O	100	2	95

4	K_2CO_3 (1.0)	H_2O	100	2	84
5	K_2CO_3 (0.5)	H_2O	100	2	50
6	No base	H_2O	100	2	0
7	NaOH (1.5)	H_2O	100	2	96
8	Et_3N (1.5)	H_2O	100	2	58
9	NH_4OH (1.5)	H_2O	100	2	20
10	Cs_2CO_3 (1.5)	H_2O	100	2	96
11	K_2CO_3 (1.5)	H_2O	100	2	95
12	K_2CO_3 (1.5)	H_2O	80	2	70
13	K_2CO_3 (1.5)	H_2O	rt (28)	2	0
14	K_2CO_3 (1.5)	H_2O	rt (28)	6	15
15	K_2CO_3 (1.5)	H_2O	rt (28)	12	20
16	K_2CO_3 (1.5)	H_2O	rt(28)	24	20
17[a]	**K_2CO_3 (1.5)**	**H_2O**	**100**	**1.5**	**95**
18	K_2CO_3 (1.5)	H_2O	100	1	87
19	K_2CO_3 (1.5)	H_2O	100	30 min	43
20	K_2CO_3 (1.5)	H_2O	100	15 min	10
21	K_2CO_3 (1.5)	H_2O:EtOH (1:1)	100	1.5	65
22	K_2CO_3 (1.5)	ETOH	100	1.5	50
23	K_2CO_3 (1.5)	CH_3CN	100	1.5	78
24	K_2CO_3 (1.5)	DMSO	100	1.5	70
25	K_2CO_3 (1.5)	DMF	100	1.5	60
26	K_2CO_3 (1.5)	DCE	100	1.5	0
27	K_2CO_3 (1.5)	Toluene	100	1.5	0

Reaction conditions: Barbituric acid (1 mmol, 0.128 g) and 4-*N,N′*-dimethylaminobenzaldehyde (1 mmol, 0.149 g), 6-amino-1,3-dimethylaminouracil (1 mmol, 0.155 g), base, solvent, temperature.
[a]Best reaction conditions

This study helped us to deduce the optimised reaction conditions, which could be applied for the synthesis of the mentioned class of compounds. The optimised reaction scheme is shown in **Scheme 2.1.2**.

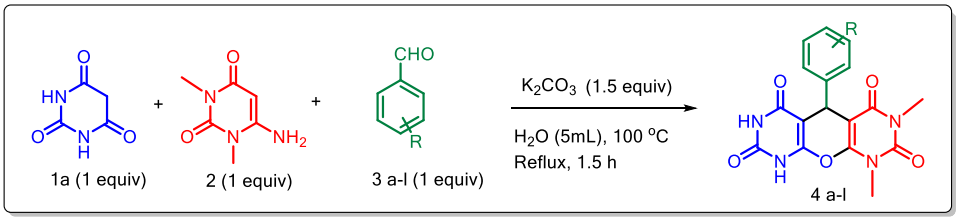
Using the optimised reaction conditions, the efficiency of the protocol was studied for the synthesis of various 5-aryl-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d′*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraones and their thioxo analogous. In most

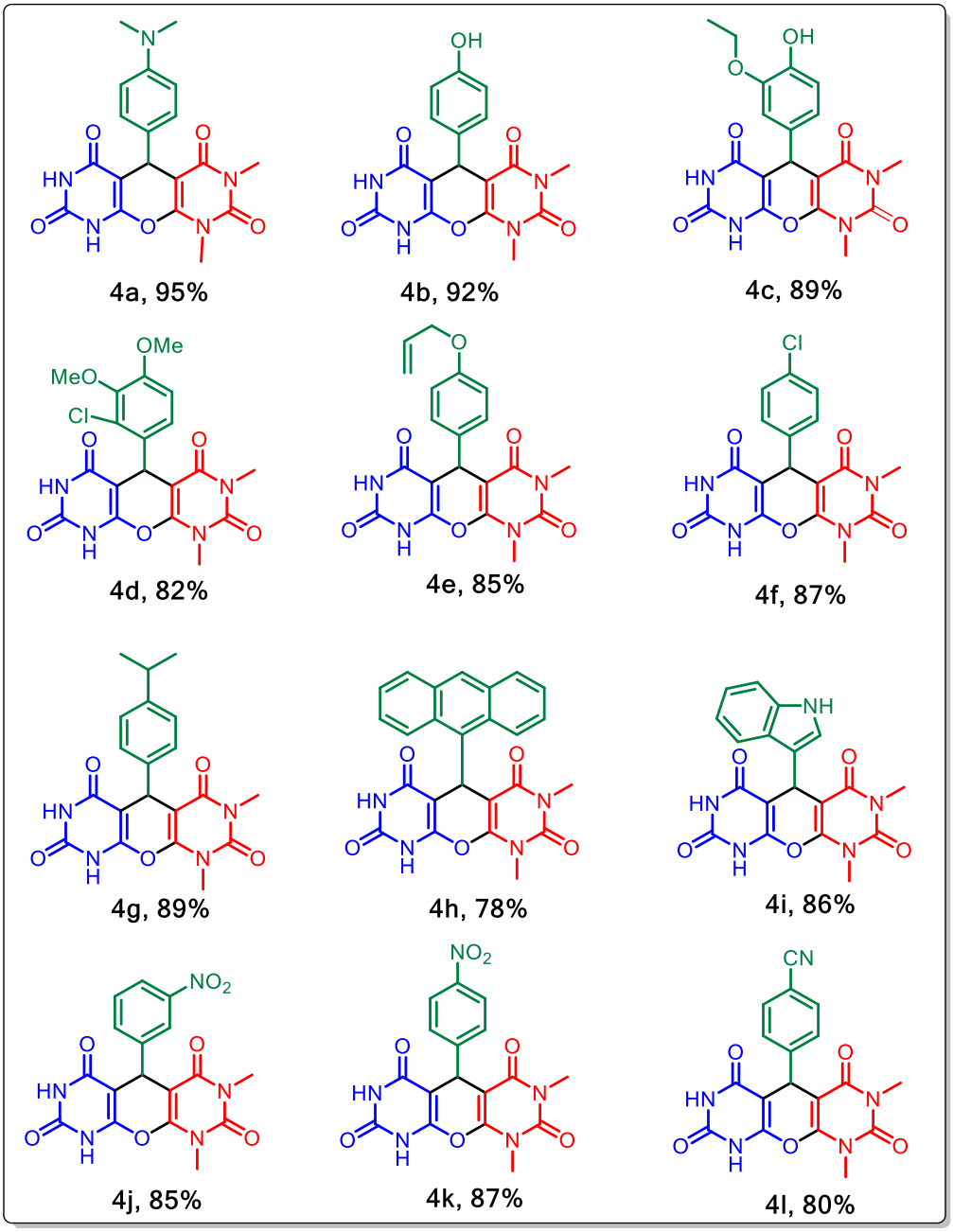


Scheme 2.1.2 Optimised reaction scheme for synthesis of unsymmetrical pyranodipyrimidines

of the cases, the reaction proceeded with high efficiency and showed broad functional group tolerance (**scheme 2.1.3** and **2.1.4**). It was observed that the presence of electron withdrawing groups or electron donating groups on the aromatic ring of the aldehydes hardly affected the rate of the reaction as the yield for both types were comparable and no significant decrease or increase was observed. However, when the aldehyde contained bulky functionalities, then there was a noticeable decrease in the yield. This could be because of the hindrance provided by the steric bulk to the approach of the 6-aminouracil moiety for Michael addition. It must also be noted here that in such case, some amount of the arylidene barbiturate remained in the final reaction mixture and was removed from the products *via* washing with dichloromethane. Dichloromethane selectively dissolved the arylidene barbiturate and not the pyranodipyrimidines, which was only soluble in highly polar solvents like DMSO. Unfortunately, when some aliphatic aldehydes such as cinnamaldehyde, acetaldehyde, glucose and formaldehyde were used in this protocol under the optimised conditions, the desired products could not be obtained. Moreover, the reaction fails when aromatic ketones or aliphatic ketones are used instead of the aldehydes. Aromatic ketones did not participate in the Knoevenagel reaction under the given

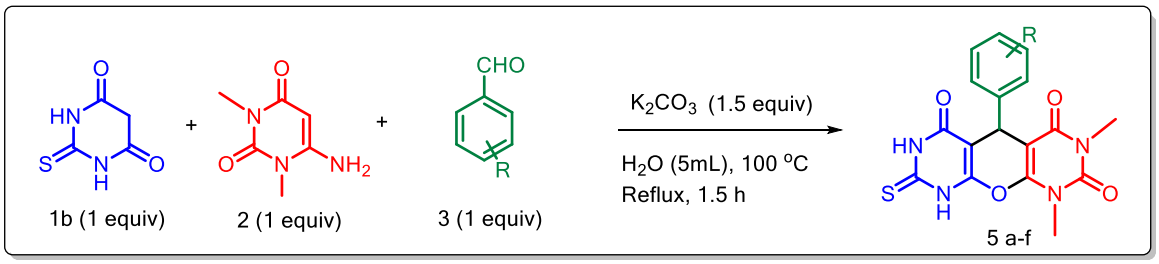
Scheme 2.1.3 Substrate study for the synthesis of 5-aryl-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraones

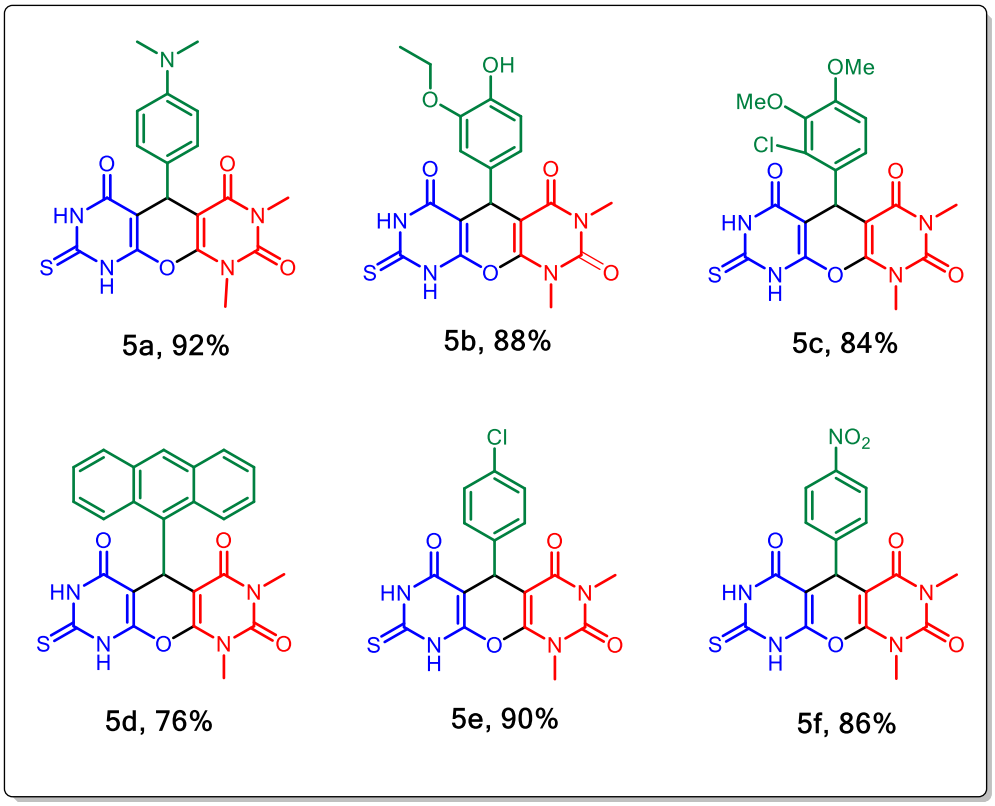




Reaction conditions: Barbituric acid (1 mmol) and aromatic aldehyde (1 mmol), 6-amino-1,3-dimethylaminouracil (1 mmol), K_2CO_3 (1.5 mmol), H_2O (5 mL), 100 °C (reflux), 1.5 h.

Scheme 2.1.4 Substrate study for the synthesis of 1,3-dimethyl-5-aryl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione



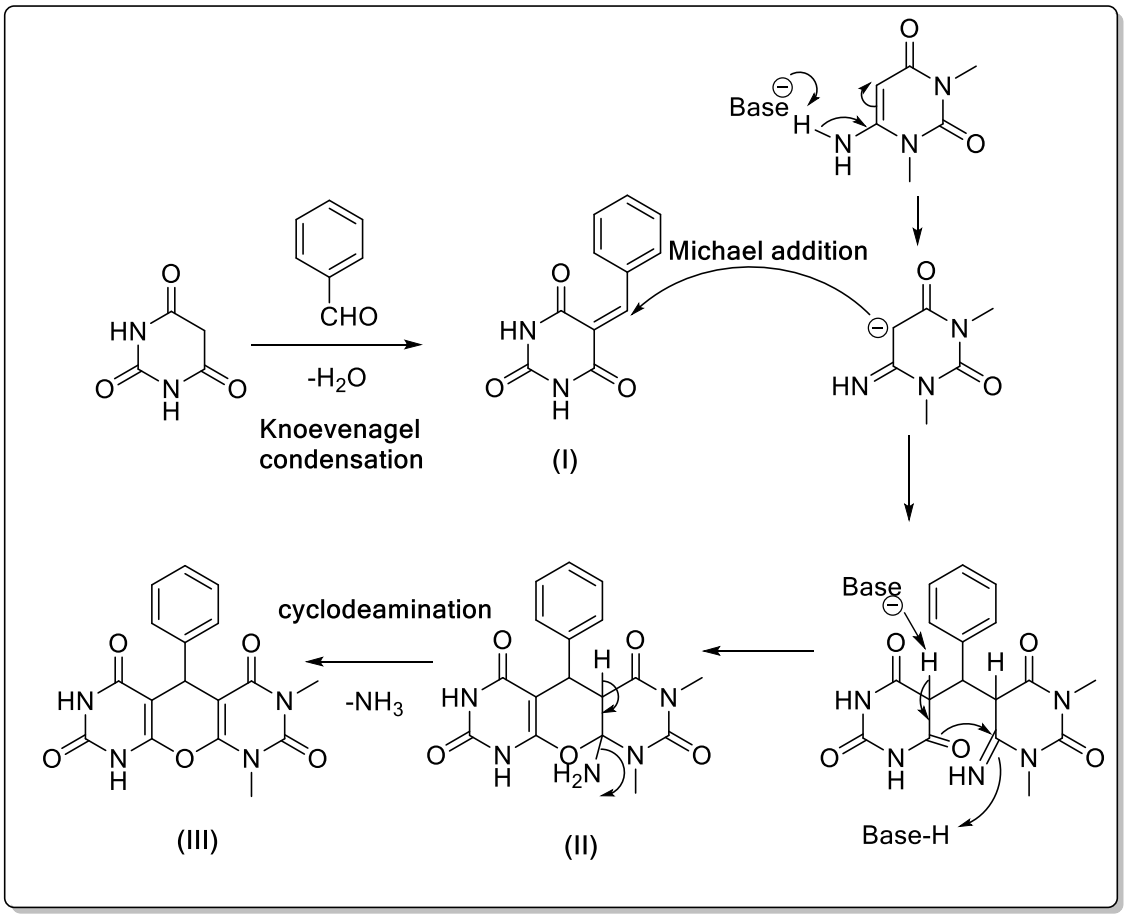


Reaction conditions: Thiobarbituric acid (1 mmol) and aromatic aldehyde (1 mmol), 6-amino-1,3-dimethylaminouracil (1 mmol), K_2CO_3 (1.5 mmol), H_2O (5 mL), 100 °C (reflux), 1.5 h

conditions and the aliphatic cyclic ketones bore the steric bulk and hindered the attack of the 6-aminouracils.

The plausible mechanism for the base driven domino synthesis of 5-aryl-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraones and their thioxo analogous can be shown to proceed through a three step route (**Scheme 2.1.5**). First, the barbituric acid and the aromatic aldehyde

undergo a Knoevenagel condensation to form 5-arylidene barbiturate (I) intermediate. This is an 1,3-unsaturated carbonyl and therefore, in the presence of the base there is a nucleophillic attack by the 6-aminouracil to result in a cyclised pyran ring, with the $–NH_2$ group still attached to the uracil parent moiety (II). This step is the initiator of the cyclodeamination step. Lastly, a deamination step occurs to result in the desired product (III).



Scheme 2.1.5 Plausible mechanism for base mediated synthesis of unsymmetrical pyranodipyrimidine

2.1.3. 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. Additional signal at 3.30 ppm, in ^{1}H 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, “br” = broad 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-aryl-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraones (4a-l) and 1,3-dimethyl-5-aryl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-triones (5a-f)

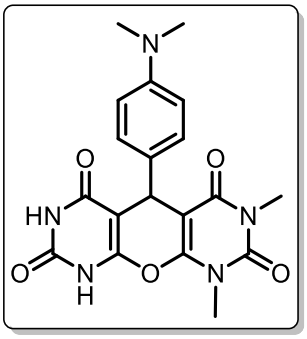
In a round bottomed flask, Barbituric acid or Thiobarbituric acid (1 equiv), aromatic aldehyde (1 equiv) and 6-amino-1,3-dimethylaminouracil (1 equiv) was added to form a slurry with 5 mL distilled H_2O. It was stirred until the formation of 5-arylidene barbiturate or thiobarbiturate was confirmed by the change in colour

of the slurry. After this, K_2CO_3 (1.5 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 1.5 hours. After the completion of the reaction, as indicated by thin layer chromatography, the reaction mixture was cooled and filtered off. The precipitate was washed with ethanol and dichloromethane and dried under vacuum. It was then characterized without further purification.

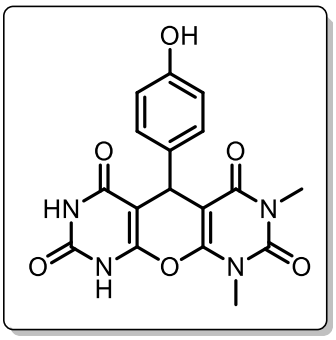
2.1.4 CONCLUSION

In conclusion it can be stated that an efficient methodology for the synthesis of 5-aryl-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraones and 1,3-dimethyl-5-aryl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-triones was developed. The protocol successfully achieved the formation of unsymmetrical pyranodipyrimidines under basic conditions. It is a novel methodology developed for the synthesis of unsymmetrical pyranodipyrimidines *via* one-pot domino approach. The products formed were isolated through chromatography free method, i.e., by simple filtration, in high purity and the yields obtained were good to excellent. Also, the reaction protocol does not suffer from the formation of any side products despite the presence of highly reactive substrates. Moreover, the protocol developed was green and exhibited good atom economy. Additionally, the target of accomplishing MCRs on-water was also achieved.

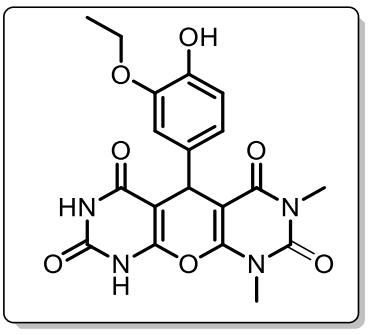
2.1.5 CHARACTERISATION DATA OF THE PRODUCTS



5-(4-(dimethylamino)phenyl)-1-methyl-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 (364.01 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.23 (s, 1H), 11.01 (s, 1H), 7.33 – 7.18 (m, 2H), 6.81 – 6.67 (m, 2H), 4.58 (s, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 2.88 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 170.6, 168.6, 167.8, 165.4, 150.8, 149.4, 146.4, 128.4, 125.9, 112.0, 107.3, 92.8, 51.3, 42.0, 29.7, 29.1. **HRMS (+ESI)** calcd for $C_{19}H_{19}N_5O_5$ $(M+H)^+$: 383.1386, found: 383.1397

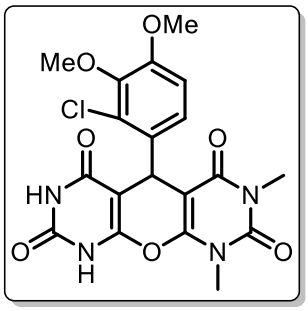


5-(4-hydroxyphenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4b) Pale yellow solid (340.52 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.45 (s, 1H), 11.25 (s, 1H), 7.32 – 7.18 (m, 2H), 6.92 – 6.77 (m, 2H), 5.64 (s, br, 1H), 4.34 (s, 1H), 3.15 (s, 3H), 2.88 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 170.7, 169.3, 167.2, 165.8, 153.4, 147.4, 144.1, 129.3, 128.5, 115.3, 103.0, 92.8, 50.1, 30.1, 28.5. **HRMS (+ESI)** calcd for $C_{17}H_{14}N_4O_6$ $(M+H)^+$: 370.0913, found: 370.0915

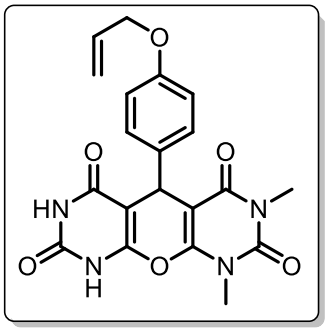


5-(3-ethoxy-4-hydroxyphenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4c) Yellow solid (368.60 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.38 (s, 1H), 10.58 (s, 1H) 7.10 (s, 1H), 6.85 (d, *J*= 7.8 Hz, 1H), 6.74 (d, *J*= 7.8 Hz, 1H), 4.78 (s, 1H), 4.28 (s, br, 1H), 4.11 – 3.99 (m, 2H), 3.13 (s, 3H), 2.85 (s, 3H), 1.37 (t, *J*= 6.2 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ

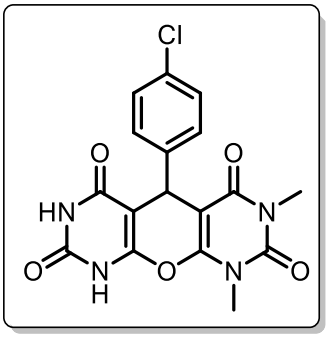
168.6, 167.3, 165.7, 160.3, 149.4, 147.8, 147.6, 142.1, 129.3, 119.5, 117.6, 115.3, 103.0, 92.8, 64.5, 51.7, 30.9, 28.7, 13.8. **HRMS (+ESI)** calcd for $C_{19}H_{18}N_4O_7$ $(M+H)^+$: 414.1175, found: 414.1186



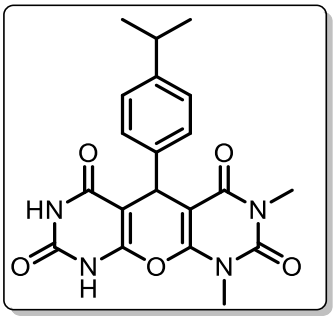
5-(2-chloro-3,4-*d*imethoxyphenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4d) Yellow solid (367.44 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.29 (s, 1H), 10.87 (s, 1H), 7.33 (s, 1H), 6.97 (s, 1H), 4.60 (s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.11 (s, 3H), 2.88 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 166.6, 164.3, 163.9, 162.1, 151.3, 148.0, 147.7, 142.3, 131.7, 128.0, 122.9, 113.3, 102.4, 92.8, 60.6, 56.7, 48.3, 30.4, 27.4. **HRMS (+ESI)** calcd for $C_{19}H_{17}ClN_4O_7$ $(M+H)^+$: 448.0286, found: 448.0307



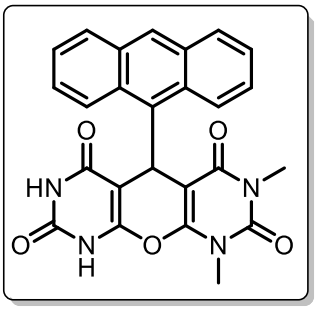
5-(4-(allyloxy)phenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4e) White solid (349.01 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.19 (s, 1H), 11.01 (s, 1H), 7.35 – 7.21 (m, 4H), 5.38 (d, J = 3.8 Hz, 1H), 5.11 (d, J = 3.4 Hz, 2H), 4.54 (d, J = 4.2 Hz 1H), 4.45 (s, 1H), 3.10 (s, 3H), 2.93 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 167.5, 166.3, 165.8, 164.7, 151.3, 149.4, 144.1, 134.4, 132.9, 129.5, 117.5, 114.5, 103.0, 92.8, 70.0, 50.1, 30.4, 28.7. **HRMS (+ESI)** calcd for $C_{20}H_{18}N_4O_6$ $(M+H)^+$: 410.1226, found: 410.1239



5-(4-chlorophenyl)-1,3-dimethyl-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) White solid (377.58 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.25 (s, 1H), 10.45 (s, 1H), 7.36 – 7.21 (m, 4H), 4.39 (s, 1H), 3.11 (s, 3H), 2.88 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 167.6, 166.3, 165.7, 161.8, 149.7, 144.6, 139.5, 132.5, 130.3, 127.2, 102.3, 92.8, 50.1, 30.4, 27.5. **HRMS (+ESI)** calcd for $C_{17}H_{13}ClN_4O_5$ $(M+H)^+$: 388.0574, found: 388.0591

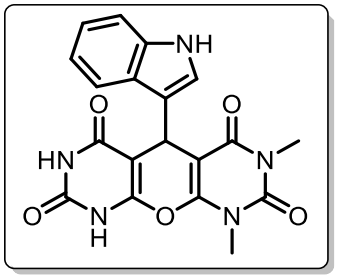


5-(4-isopropylphenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4g) White solid (352.60 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.24 (s, 1H), 10.48 (s, 1H), 7.45 – 7.31 (m, 2H), 7.31 – 7.19 (m, 2H), 4.32 (s, 1H), 3.01 (s, 3H), 2.98 (s, 1H), 2.92 – 2.88 (m, 3H), 1.37 (d, J = 6.8 Hz, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 170.6, 168.3, 165.7, 163.3, 150.9, 149.4, 147.1, 140.5, 129.9, 125.9, 103.0, 92.8, 50.3, 34.0, 30.4, 28.6, 23.5. **HRMS (+ESI)** calcd for $C_{20}H_{20}N_4O_5$ $(M+H)^+$: 396.1434, found: 396.1438

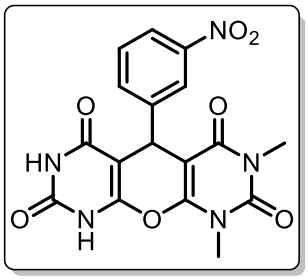


5-(anthracen-9-yl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4h) Dark red solid (354.22 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.98 (s, 1H), 10.47 (s, 1H), 8.17 (s, 1H), 7.90 – 7.79 (m, 2H), 7.79 – 7.68 (m, 2H), 7.37 – 7.30 (m, 4H), 4.57 (s, 1H), 3.16 (s, 3H), 2.84 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 169.6, 168.2, 166.7, 164.3, 148.0,

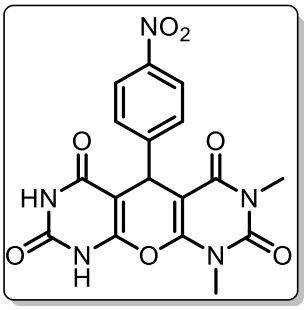
142.8, 132.4, 130.2, 129.1, 127.7, 127.2, 125.9, 124.5, 102.0, 93.7, 58.3, 30.4, 28.7. **HRMS (+ESI)** calcd for $C_{25}H_{18}N_4O_5$ $(M+H)^+$: 454.1277, found: 454.1293



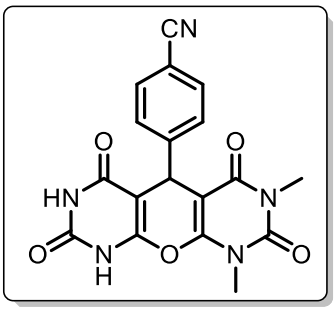
5-(1*H*-indol-3-yl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4i) Brown solid (338.12 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.19 (s, 1H), 11.01 (s, 1H), 9.65 (s, 1H), 7.24 (d, *J* = 6.7 Hz, 2H), 7.16 - 7.08 (m, 2H), 6.77 (d, *J* = 6.8 Hz, 1H), 4.01 (s, 1H), 3.10 (s, 3H), 2.73 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 168.7, 167.3, 165.7, 163.3, 142.4, 138.6, 137.6, 126.9, 123.5, 121.4, 118.2 113.3, 109.3, 108.1, 96.3, 39.1, 30.9, 27.6. **HRMS (+ESI)** calcd for $C_{19}H_{15}N_5O_5$ $(M+H)^+$: 393.1073, found: 393.1097



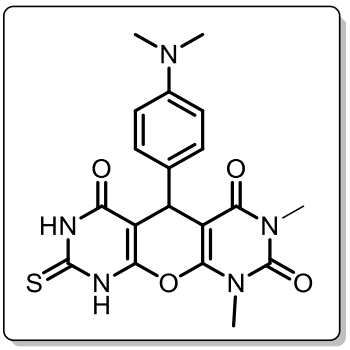
1,3-dimethyl-5-(3-nitrophenyl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4j) Yellow solid (338.96 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.87 (s, 1H), 10.54 (s, 1H), 8.00 (d, *J* = 5.4 Hz, 1H), 7.88 (s, 1H), 7.54 – 7.28 (m, 2H), 4.52 (s, 1H), 3.03 (s, 3H), 2.82 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 168.6, 166.3, 165.9, 163.6, 149.4, 147.6, 144.3, 139.4, 136.1, 129.4, 127.9, 124.1, 103.0, 92.8, 51.7, 30.3, 28.1. **HRMS (+ESI)** calcd for $C_{17}H_{13}N_5O_7$ $(M+H)^+$: 399.0815, found: 399.0831



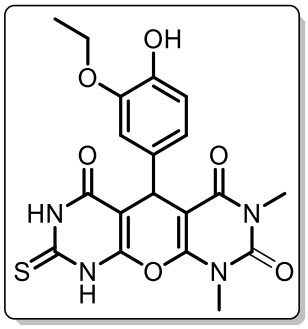
1,3-dimethyl-5-(4-nitrophenyl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4k) Yellow solid (347.25 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.25 (s, 1H), 10.94 (s, 1H), 8.22 (d, *J*= 8.8 Hz, 2H), 7.34 (d, *J*= 8.4 Hz, 2H), 4.76 (s, 1H), 2.89 (s, 3H), 2.62 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 170.6, 168.7, 162.8, 152.9, 151.9, 151.0, 147.3, 124.3, 82.4, 81.5, 44.2, 33.0, 32.4. **HRMS (+ESI)** calcd for $C_{17}H_{13}N_5O_7$ $(M+H)^+$: 399.0815, found: 399.0827



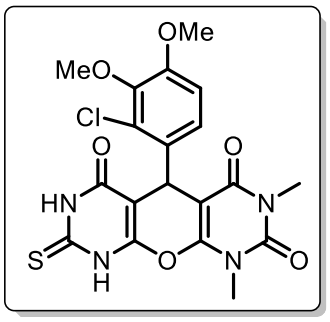
4-(1,3-dimethyl-2,4,6,8-tetraoxo-1,3,4,5,6,7,8,9-octahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidin-5-yl)benzonitrile (4l) White solid (303.33 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.88 (s, 1H), 10.72 (s, 1H), 7.69 – 7.55 (m, 2H), 7.55 – 7.49 (m, 2H), 4.53 (s, 1H), 3.12 (s, 3H), 2.88 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 164.2, 162.7, 158.7, 154.3, 149.4, 146.5, 143.1, 131.3, 130.1, 119.1, 114.6, 103.0, 92.8, 50.1, 33.9, 26.6. **HRMS (+ESI)** calcd for $C_{18}H_{13}N_5O_5$ $(M+H)^+$: 379.0917, found: 379.0928



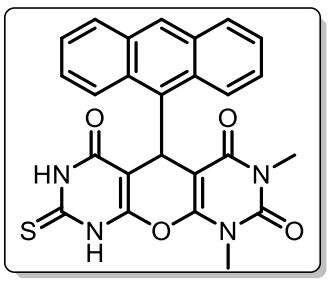
5-(4-(dimethylamino)phenyl)-1-methyl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (5a) Pink solid (366.85 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.65 (s, 1H), 10.24 (s, 1H), 7.32 – 7.18 (m, 2H), 6.80 – 6.66 (m, 2H), 5.21 (s, 1H), 3.79 (s, 3H), 3.56 (s, 3H), 2.88 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 172.6, 162.3, 155.9, 151.6, 149.8, 145.9, 142.1, 129.1, 126.5, 123.9, 123.8, 103.0, 92.8, 50.1, 30.9, 28.7. **HRMS (+ESI)** calcd for $C_{18}H_{17}N_5O_4S$ $(M+H)^+$: 399.1001, found: 399.1015



5-(3-ethoxy-4-hydroxyphenyl)-1,3-dimethyl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (5b) Pink solid (378.62 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.25 (s, 1H), 10.45 (s, 1H), 8.64 (s, 1H), 7.05 (s, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 6.65 (d, *J*= 8.2 Hz, 1H), 4.48 (s, 1H), 4.14 – 4.02 (m, 2H), 3.87 (s, 3H), 3.15 (s, 3H), 1.44 (d, *J*= 6.8 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.4, 162.3, 159.5, 155.7, 152.2, 147.8, 147.6, 144.1, 129.3, 119.7, 117.4, 115.9, 103.0, 95.1, 64.5, 51.7, 30.9, 28.6, 13.3. **HRMS (+ESI)** calcd for $C_{19}H_{18}N_4O_6S$ $(M+H)^+$: 430.0947, found: 430.0954

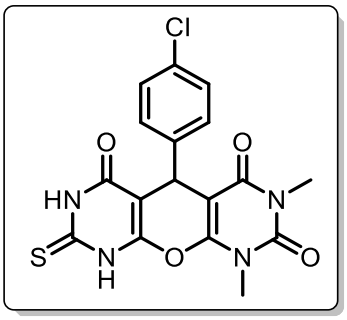


5-(2-chloro-3,4-dimethoxyphenyl)-1,3-dimethyl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (5c) Dark yellow solid (389.91 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.20 (s, 1H), 10.98 (s, 1H), 7.87 (s, 1H), 7.12 (s, 1H), 4.37 (s, 1H), 3.76 (s, 3H), 3.09 (s, 3H), 2.92 (s, 3H), 2.88 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.4, 162.3, 159.0, 155.9, 152.4, 150.4, 148.0, 144.7, 131.7, 128.0, 122.4, 113.6, 102.9, 93.2, 60.5, 56.7, 48.3, 31.4, 26.7. **HRMS (+ESI)** calcd for $C_{19}H_{17}ClN_4O_6S$ $(M+H)^+$: 464.0557, found: 464.0572

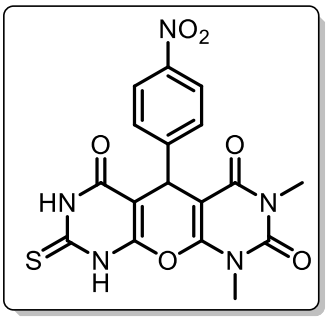


5-(anthracen-9-yl)-1,3-dimethyl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (5d) Dark red solid (356.98 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.38 (s, 1H), 10.27 (s, 1H), 8.14 (s, 1H), 7.90 – 7.82 (m, 2H), 7.79 – 7.56 (m, 2H), 7.39 – 7.32 (m, 4H), 4.61 (s, 1H), 3.21 (s, 3H), 2.92 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.4, 166.3, 159.5, 154.7, 143.3, 141.8, 135.5,

130.0, 129.1, 127.7, 127.2, 125.5, 124.7, 102.4, 95.6, 58.8, 31.4, 27.6. **HRMS (+ESI)** calcd for $C_{25}H_{18}N_4O_4S$ $(M+H)^+$: 470.1049, found: 470.1053



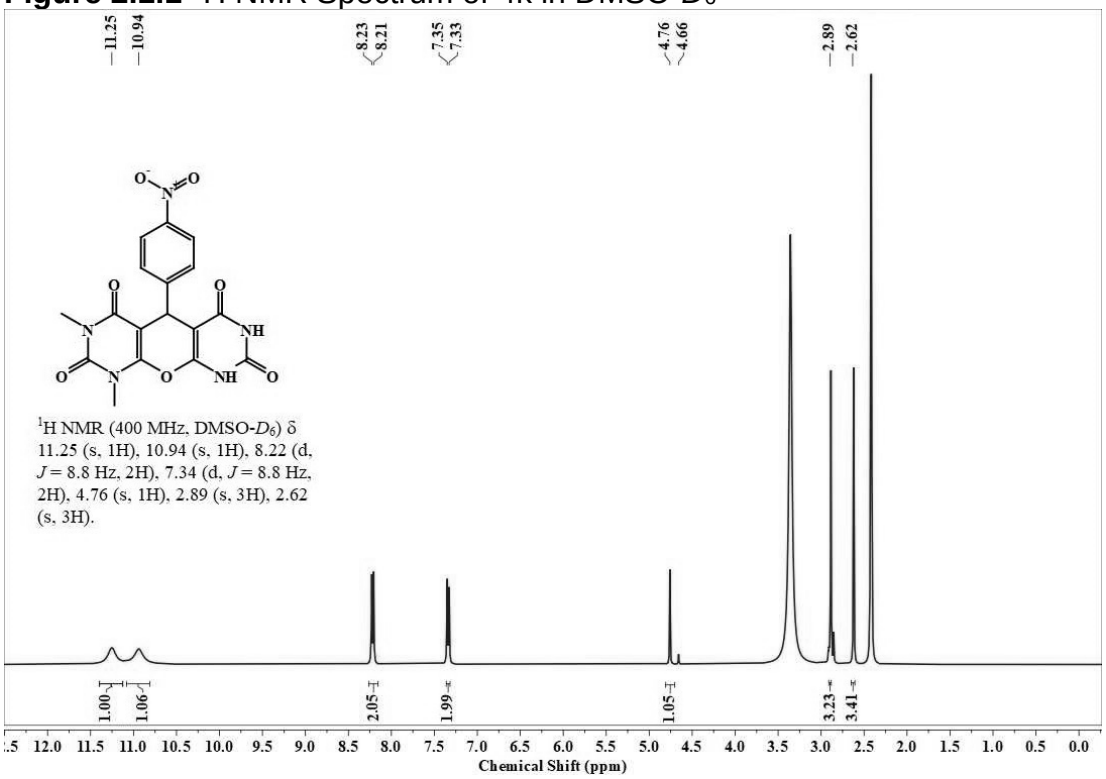
5-(4-chlorophenyl)-1,3-dimethyl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (5e) Pale pink solid (363.69 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.36 (s, 1H), 10.64 (s, 1H), 7.39 – 7.29 (m, 2H), 7.29 – 7.20 (m, 2H), 4.51 (s, 1H), 3.10 (s, 3H), 2.92 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 176.4, 167.3, 158.5, 154.7, 151.2, 143.1, 132.5, 130.5, 130.3, 123.8, 103.3, 95.1, 50.1, 33.4, 27.7. **HRMS (+ESI)** calcd for $C_{17}H1_3ClN_4O_4S$ $(M+H)^+$: 404.0346, found: 404.0361



1,3-dimethyl-5-(4-nitrophenyl)-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (5f) Orange solid (356.85 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.46 (s, 1H), 11.25 (s, 1H), 8.07 – 7.92 (m, 2H), 7.69 – 7.55 (m, 2H), 4.43 (s, 1H), 3.15 (s, 3H), 2.85 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 177.4, 165.3, 158.5, 154.7, 153.2, 148.3, 145.6, 143.1, 129.1, 123.2, 103.3, 95.6, 50.3, 32.4, 27.7. **HRMS (+ESI)** calcd for $C_{17}H_{13}N_5O_6S$ $(M+H)^+$: 415.0587, found: 415.0604

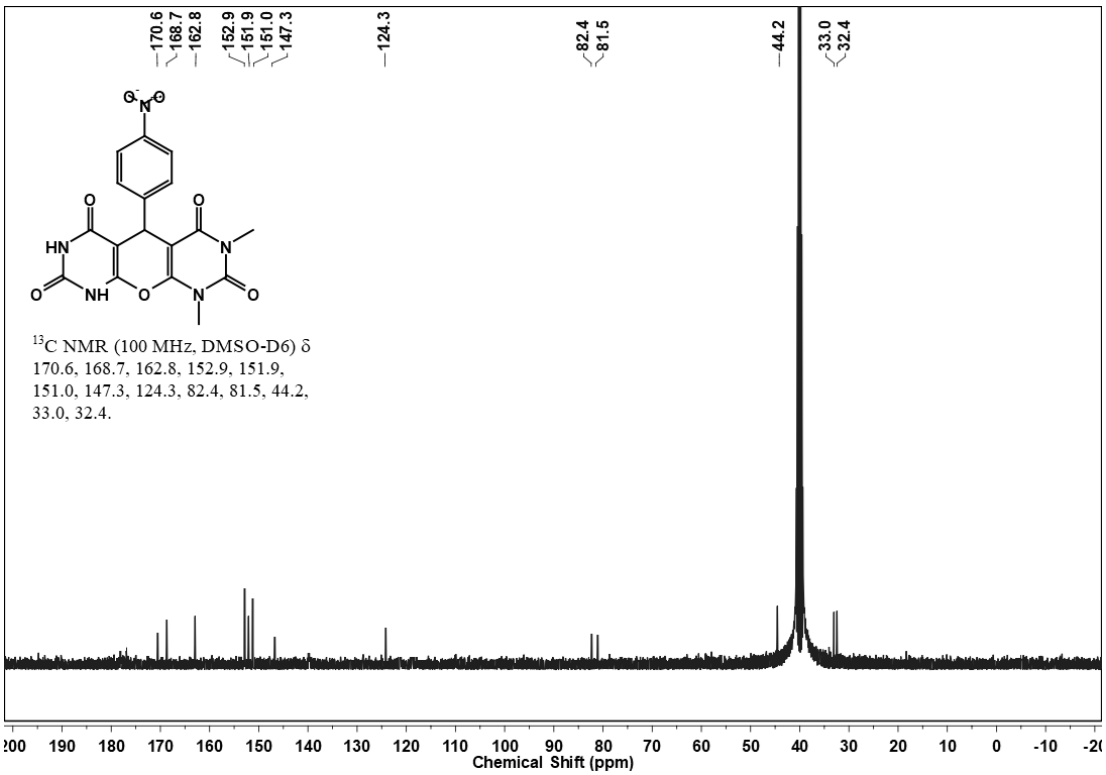
2.1.6 REPRESENTATIVE NMR SPECTRA

Figure 2.1.1 ^{1}H NMR Spectrum of 4k in DMSO-D_6



^{1}H NMR (400 MHz, DMSO-D_6) δ 11.25 (s, 1H), 10.94 (s, 1H), 8.22 (d, J = 8.8 Hz, 2H), 7.34 (d, J = 8.8 Hz, 2H), 4.76 (s, 1H), 2.89 (s, 3H), 2.62 (s, 3H).

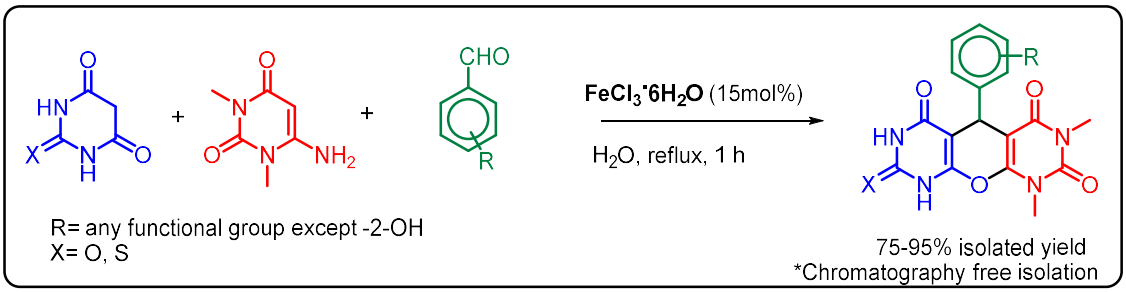
Figure 2.1.2 ^{13}C NMR Spectrum of 4k in DMSO-D_6



^{13}C NMR (100 MHz, DMSO-D6) δ 170.6, 168.7, 162.8, 152.9, 151.9, 151.0, 147.3, 124.3, 82.4, 81.5, 44.2, 33.0, 32.4.

SECTION 2.2

$FeCl_3 \cdot 6H_2O$ catalysed "on-water" synthesis of unsymmetrical 5-aryl-pyranodipyrimidines



2.2.1 INTRODUCTION

Owing to the potential pharmaceutical value of pyranodipyrimidines, it has caught the interest of researchers around the globe. However, the limited number of ways in which it can be formed has left an open ground for exploration of novel methods. In the previous section (**section 2.1**), the development of an on-water protocol for the synthesis of unsymmetrical pyranopyrimidines was reported. It was a base mediated reaction and apart from the energy consumption factor (which is unavoidable in many synthetic methodologies), the usage of stoichiometric amount of base can be counted as the prime short coming. This brings about the need for suitable catalysts which can produce considerably good yields along with the other onuses. It was observed that a base could not catalyse the mentioned transformation to produce satisfactory yields and therefore, experimenting with the available basic catalysts was never on the cards. Hence, the answer for the suitable catalyst was sought in the acid category, which could not only selectively direct the formation of the pyran- ring (as literature reports the formation of pyrido- ring instead, in the presence of acids) but aid the completion of the reaction in greener media.

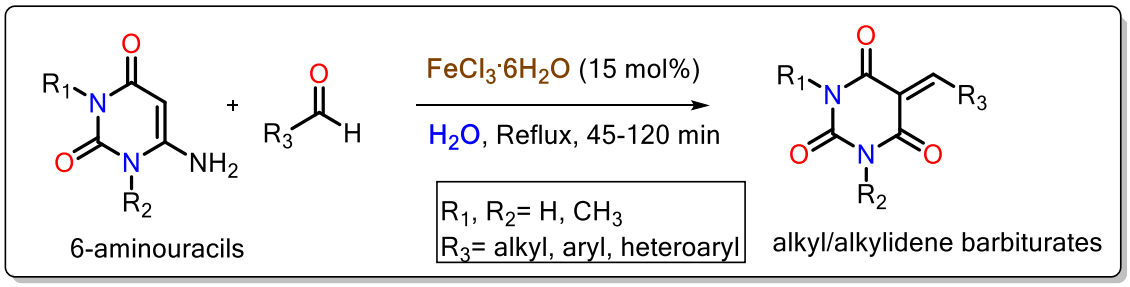
Our endeavor to develop multicomponent reactions in aqueous environment confronted us with iron catalysts- a cheap, versatile and highly efficient class of compounds. These catalysts have been known to catalyse organic transformations in both homogeneous and heterogeneous reaction media and show tolerance to a wide range of conditions and functionalities. Also, their utility in diversified reactions such as addition, substitution, cycloaddition, and

polymerization is noteworthy [36]. Iron(III)chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) especially, has played the role of a Lewis acid catalyst in organic synthesis since long times. Additionally, it is an economically viable, environmentally benign and easy to handle catalyst [36,43].

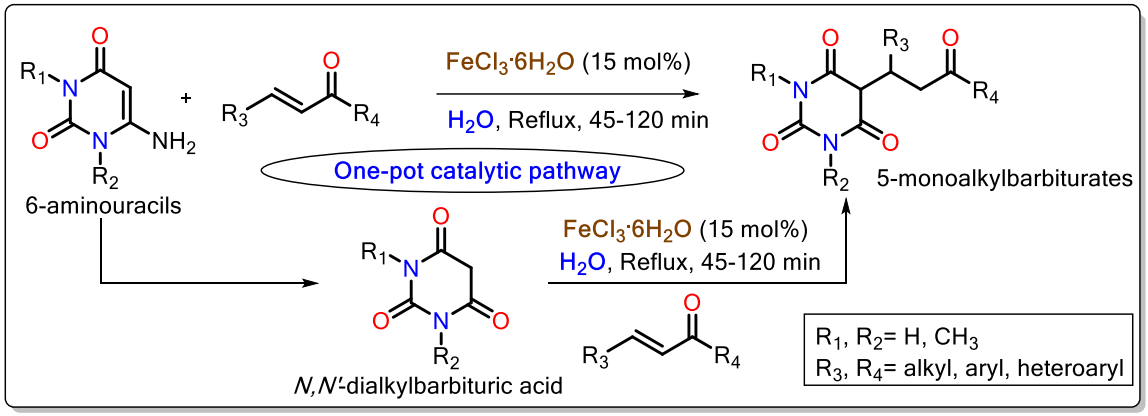
The common challenge en route to pyranodipyrimidines is the specific nucleophillic attack of 6-aminouracil to the exo-double bond of benzylidene barbiturate and subsequent deamination. The presence of an acid catalyst prevents the deamination step to take place and instead favours dehydration followed by cyclisation, which results in the formation of the pyrido ring [44,45]. However, if the amino group can be replaced by a carbonyl group, then the dehydration will lead to the formation of the pyran ring. Also, to make things easier if two different barbituric acids are used, then there will be formation of symmetrical pyranodipyrimidines along with the unsymmetrical analogue and will make separation difficult. Thus, to achieve the target of forming unsymmetrical pyranodipyrimidines, we are left with the options of using 6-aminouracil and barbituric acids as the reactants. But, in due course of the reaction if the amino group of 6-aminouracil is converted into a carbonyl group, and then the reaction will proceed towards the formation of the desired molecule.

Keeping our hypothesis in mind along with an aim to use cheap acid catalyst such as $FeCl_3 \cdot 6H_2O$, we surveyed through reported literatures and came across two protocols reported by Kalita *et al.* which were published in 2013 and 2014 respectively (**Schemes 2.2.1** and **2.2.2**) [46, 47]. The utilization of $FeCl_3 \cdot 6H_2O$ as catalyst and water as a solvent as well as reagent for the synthesis of 5-

monoalkylbarbiturates was shown. The interesting point to note here was the usage of 6-aminouracils instead of barbituric acids. Also, it was seen that the reaction proceeded through an *in situ* conversion of 6-aminouracils to barbituric acids in the presence of the catalyst and water under reflux conditions. This solidified the foundation of our hypothesis and inspired to design a $FeCl_3{\cdot}6H_2O$ catalysed synthesis of pyranodipyrimidines in water where the *in situ* conversion of 6-aminouracils to barbituric acids could be incorporated as a crucial step followed by dehydrogenative cyclisation to form the required pyran ring with two different pyrimido rings fused to it.



Scheme 2.2.1 Reaction of 6-aminouracils with aldehydes in water under $FeCl_3{\cdot}6H_2O$ catalysis towards formation of 5-alkyl/arylidenebarbituric acids (Kalita *et al.*)



Scheme 2.2.2 $FeCl_3{\cdot}6H_2O$ catalysed aqueous media domino synthesis of 5-monoalkylbarbiturates (Kalita *et al.*)

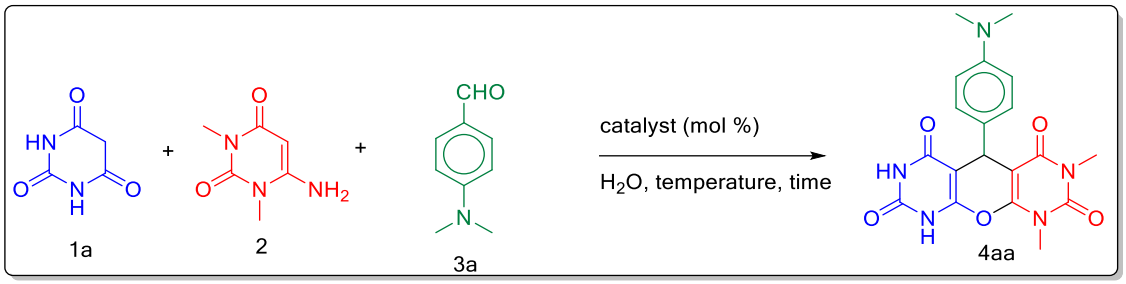
2.2.2 RESULTS AND DISCUSSION

Following the hypothesis, an initial experimentation with $FeCl_3 \cdot 6H_2O$ catalysed, on-water synthesis of pyranodipyrimidines was conducted. For this a round bottomed flask was charged with a mixture of barbituric acid (1 mmol) (**1a**), 4-*N,N'*-dimethylaminobenzaldehyde (1 mmol) (**3a**) and 1,3-dimethyl-6-aminouracil (1 mmol) (**2**) to form a slurry in distilled water (5 mL). The reaction mixture was stirred at room temperature until the Knoevenagel condensation between barbituric acid and the aldehyde was complete to form the corresponding benzylidene barbiturate. This was evident from the deep orange colouration of the slurry. Following this, 10 mol% $FeCl_3 \cdot 6H_2O$ was added to the reaction mixture and stirring was continued under reflux for 3 hours, with intermittent observation of the progress of the reaction *via* TLC. It was observed that the desired product i.e. 5-(4-(dimethylamino)phenyl)-1-methyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (**4aa**) was formed at the end of the reaction and the preliminary confirmation was made by comparing the retention factor of the formed compound with the one previously formed in section 2.1 (**4a**) through TLC. The product was also isolated by simple filtration and washed with dichloromethane (DCM), Ethanol and finally with distilled water. The pale yellow precipitate was dried under vacuum to give 82% isolated yield. It is a point to note here that the product formed precipitated out and no chromatographic separation was required to isolate it. The product was later analysed with the help of ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The presence of the characteristic –CH proton peak of the pyran ring, showing resonance at δ 4.58

ppm and the tertiary methyl carbon of the pyran ring showing resonance at δ 51.3 ppm in the ^{13}C NMR spectrum along with four different signals for the carbonyl carbons at δ 170.6, 168.6, 167.8, and 165.4 ppm, confirmed the formation of the desired unsymmetrical pyranodipyrimidine. This was further ascertained by the mass spectrum showing a molecular ion peak at m/z 383.1389 $(M+H)^+$, which correlated with its molecular formula: $C_{19}H_{19}N_5O_5$. Now, with these encouraging results other metal based Lewis acids like $CuCl_2{\cdot}2H_2O$, $NiCl_2{\cdot}6H_2O$, $CoCl_2{\cdot}6H_2O$, $AlCl_3$, were also explored as possible alternatives to $FeCl_3{\cdot}6H_2O$. It was only $FeCl_3{\cdot}6H_2O$ which gave satisfactory results. Other substances such as Amberlyst-15A, KF-Alumina, and Montmorillonite-K10 were not used because the product formed was solid and using heterogeneous acid catalysts would only make the isolation process difficult. The difficulty in separating the product from the solid catalysts would arise because it would be soluble in DMSO only and isolating it from that solution would mount up to a tedious task. Additionally the amount of the catalyst was varied to check its effect on the yield. It was found that 15 mol% of $FeCl_3{\cdot}6H_2O$ was the optimum amount of catalyst required. No alternative solvent was sought as water produced satisfactory results. The effect of temperature and time was also studied. The reaction required reflux conditions for completion and the optimum time required was 1 hour. The results for the optimisation of the reaction are summarised in **table 2.2.1**. When the reaction was allowed to continue at room temperature for a prolonged period of time (6 hours) then the desired unsymmetrical pyranodipyrimidine was not formed. Instead a mixture of the benzylidene barbiturate (**6aa**) and *bis*uracil methane (**7aa**) (**Scheme 2.2.3**) was obtained. It can therefore be stated here that the

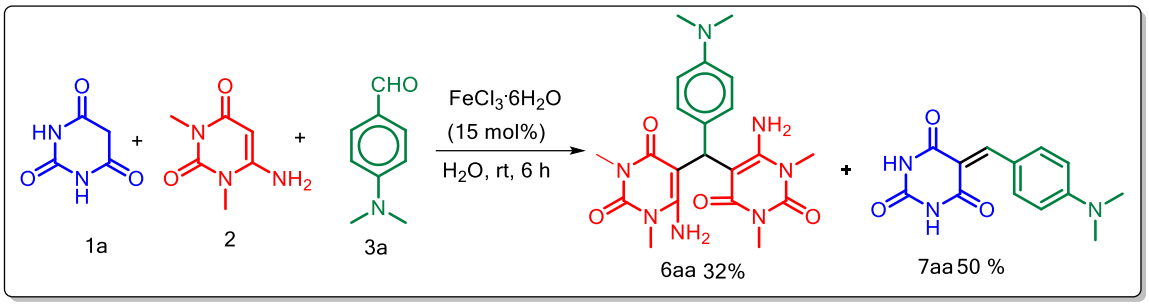
cyclisation step can take place only at elevated temperature. The protocol was extended to aromatic as well as cyclic ketones, but no results were obtained. This may be attributed to the fact that cyclic ketones or aromatic ketones offered steric resistance to the nucleophillic attack on the alkylidene/benzylidene barbiturate intermediate.

Table 2.2.1 Optimisation of the reaction



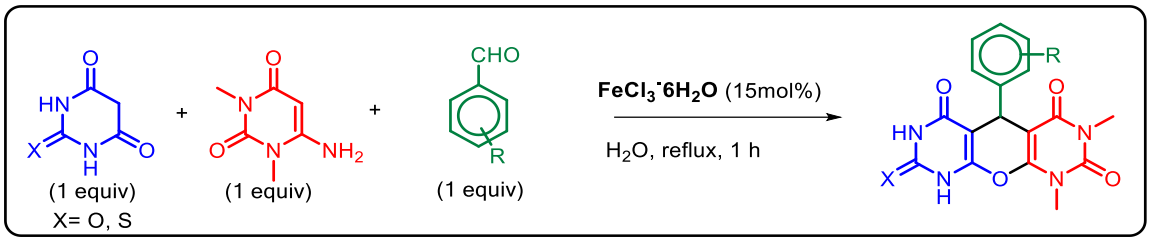
Entry	Catalyst (mol %)	Temperature °C	Time (hours)	Isolated Yield %
1	$FeCl_3{\cdot}6H_2O$ (10)	reflux	3	85
2	$FeCl_3{\cdot}6H_2O$ (10)	reflux	2	85
3	$FeCl_3{\cdot}6H_2O$ (10)	reflux	1	85
4	$FeCl_3{\cdot}6H_2O$ (10)	reflux	45 mins	81
5[a]	$FeCl_3{\cdot}6H_2O$ (15)	reflux	1	95
6	$FeCl_3{\cdot}6H_2O$ (20)	reflux	1	95
7	$FeCl_3{\cdot}6H_2O$ (25)	reflux	1	95
8	$FeCl_3{\cdot}6H_2O$ (15)	80	2	90
9	$FeCl_3{\cdot}6H_2O$ (15)	rt[c]	6	nr[b]
10	$CuCl_2{\cdot}2H_2O$ (15)	reflux	2	nr[b]
11	$NiCl_2{\cdot}6H_2O$ (15)	reflux	2	Traces
12	$CoCl_2{\cdot}6H_2O$ (15)	reflux	2	Traces
13	$AlCl_3$ (15)	reflux	2	20
14	No catalyst	reflux	2	nr[b]

Reaction conditions: Barbituric acid (1 mmol, 0.128 g) and 4-*N,N'*-dimethylaminobenzaldehyde (1 mmol, 0.149 g), 6-amino-1,3-dimethylaminouracil (1 mmol, 0.155 g), H_2O (5 mL), catalyst, temperature, time. [a]Best reaction conditions, [b]nr= no results, [c]rt= room temperature (25 °C)



Scheme 2.2.3 On-water, $FeCl_3{\cdot}6H_2O$ catalysed reaction at room temperature

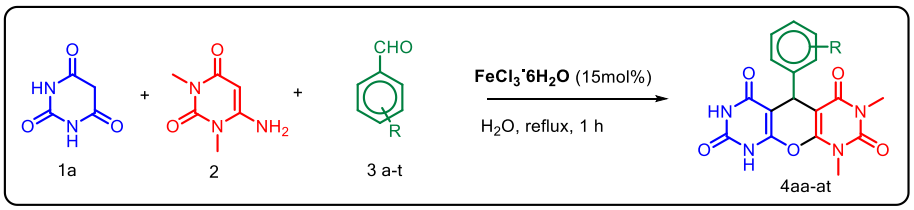
The optimized reaction scheme is shown in **scheme 2.2.4**

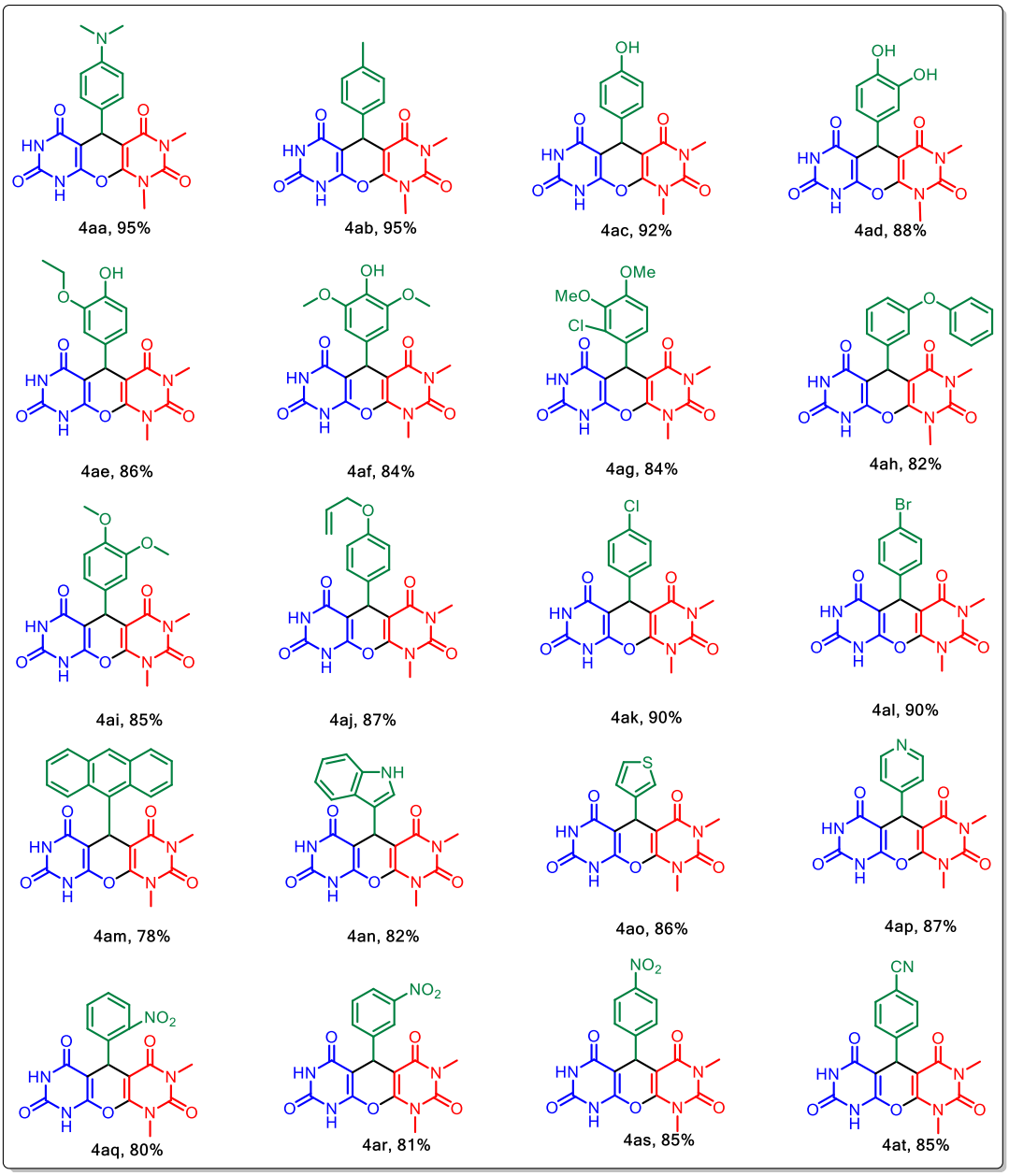


Scheme 2.2.4 Optimised reaction scheme for on-water, $FeCl_3{\cdot}6H_2O$ catalysed synthesis of unsymmetrical pyranodipyrimidines

In the next phase, the application of the reaction protocol was tested for different aromatic aldehydes bearing varied functionalities. The functionalities taken into consideration were based upon electron withdrawing and donating capacities as well as the steric bulk. As we have seen in the previous section (**section 2.1**) that the presence of bulky groups hindered the approach of the nucleophillic group towards the *exo* double bond of the benzylidene barbiturate group, the same happened in the $FeCl_3{\cdot}6H_2O$ catalysed reactions too. The yield was dependent on the steric bulk and not much was altered by the electronic factor of the substituents on the aldehyde. In short, the steric crowd around the benzylidene double bond resulted in the reduction of yield of the corresponding unsymmetrical pyranodipyrimidine. The results of the substrate study are summarized in **scheme 2.2.5**.

Scheme 2.2.5 Substrate study for on-water, $FeCl_3 \cdot 6H_2O$ catalysed synthesis of unsymmetrical pyranodipyrimidines.

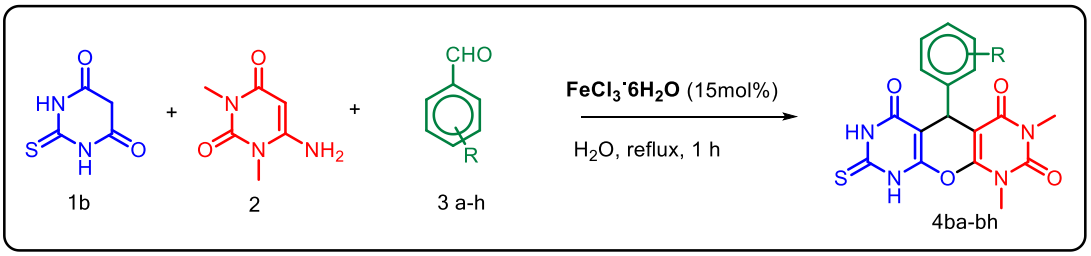


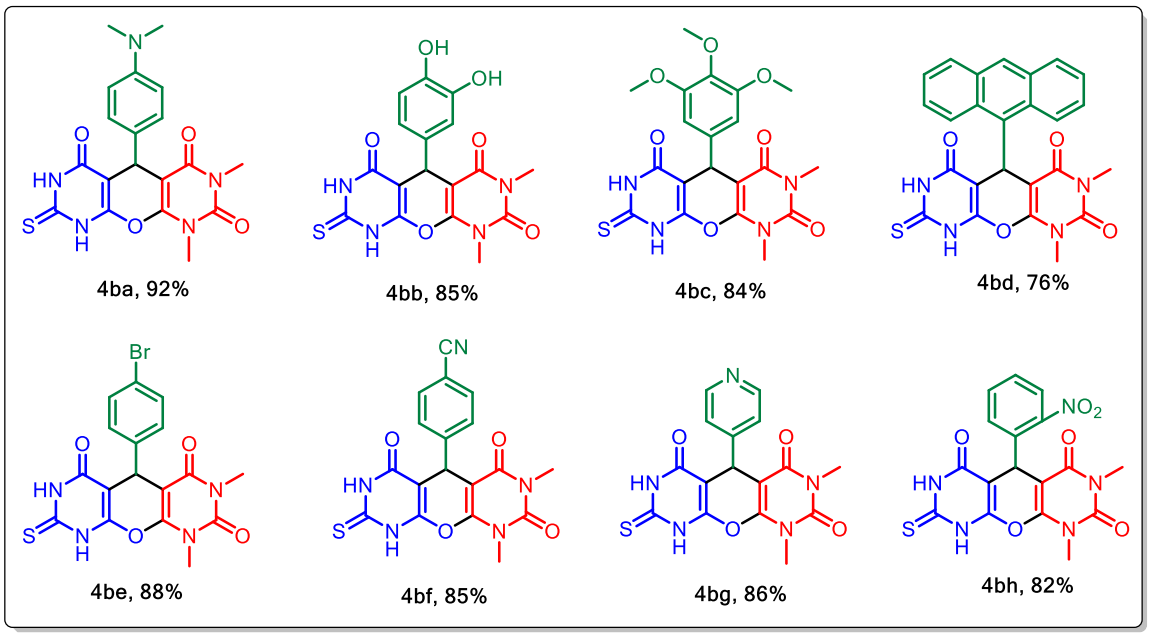


Reaction conditions: Barbituric acid (1 mmol, 0.128 g), aldehyde (1 mmol) and 6-amino-1,3-dimethylaminouracil (1 mmol, 0.155 g), H_2O (5 mL), $FeCl_3 \cdot 6H_2O$ (15 mol%, 0.0192 g), reflux, 1 h

The reaction was also carried out by using thiobarbituric acid and similar results were obtained. The study is summarized in **scheme 2.2.6**

Scheme 2.2.6 Substrate study for on-water, $FeCl_3{\cdot}6H_2O$ catalysed synthesis of unsymmetrical pyranodipyrimidines, using thiobarbituric acid

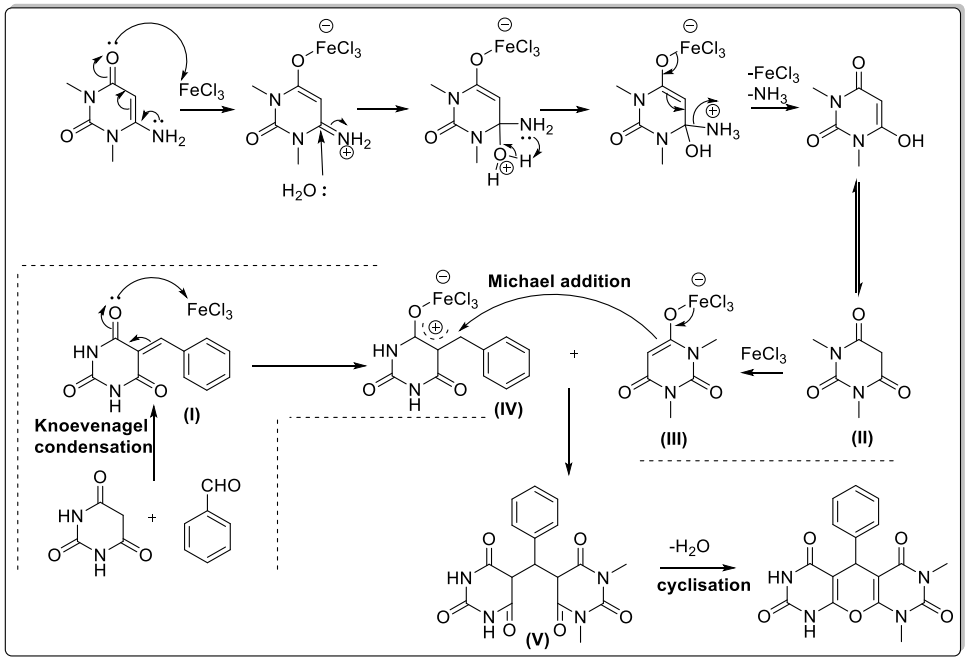




Reaction conditions: Thiobarbituric acid (1 mmol, 0.144 g), aldehyde (1 mmol) and 6-amino-1,3-dimethylaminouracil (1 mmol, 0.155 g), H_2O (5 mL), $FeCl_3{\cdot}6H_2O$ (15 mol%, 0.0192 g), reflux, 1 h

It is evident that the protocol is applicable to a wide range of substrates and the yields obtained are satisfactorily good enough to establish that this methodology is indeed efficient in achieving the targets set for the synthesis of unsymmetrical pyranodipyrimidines. Based on the obtained results, observations and literature reports [46-51], a plausible mechanism for the developed reaction protocol is

proposed in **scheme 2.2.7**. The reaction initially proceeds *via* two parallel transformations. Firstly, a faster Knoevenagel condensation between barbituric acid and the aromatic aldehyde takes place to form benzylidene barbiturate (**I**). During this time the 6-amino-1,3-dimethylaminouracil moiety acts like a spectator species. Secondly, when $FeCl_3{\cdot}6H_2O$ is added to the reaction mixture and the reaction is put under reflux, then $FeCl_3$ first coordinates to 6-amino-1,3-dimethylaminouracil and aids it in undergoing hydrolysis to transform into the corresponding barbituric acid (**II**). This *in situ* formed *N,N'*-dimethylbarbituric acid further undergoes complexation with $FeCl_3$ to form a reactive nucleophillic species (**III**). Species **III** undergoes addition reaction with a $FeCl_3$ activated benzylidene barbiturate (**IV**) to form a bisbarbiturate species (**V**). This bisbarbiturate then undergoes dehydrogenative cyclisation to form the unsymmetrical pyranodipyrimidine.



Scheme 2.2.7 Plausible mechanism for $FeCl_3{\cdot}6H_2O$ catalysed synthesis of unsymmetrical pyranodipyrimidines

2.2.3 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 dimethyl sulphoxide (DMSO-D_6, δ= 2.46 ppm, quintet, for ^{1}H and 40.0 ppm, septet, for ^{13}C) as the solvent as well 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. 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, “br” = broad 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-aryl-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d'*]dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraones (4aa-at) and 1,3-dimethyl-5-aryl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-triones (5ba-bh)

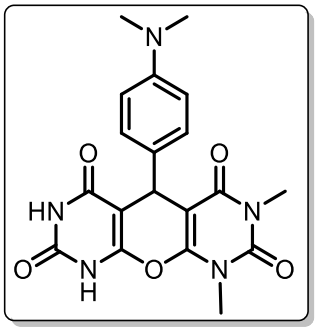
In a round bottomed flask, Barbituric acid or Thiobarbituric acid (1 equiv), aromatic aldehyde (1 equiv) and 6-amino-1,3-dimethylaminouracil (1 equiv) was added to form a slurry with 5 mL distilled H_2O. It was stirred until the formation of 5-arylidene barbiturate or thiobarbiturate was confirmed by the change in colour

of the slurry. After this, $FeCl_3 \cdot 6H_2O$ (15 mol%) 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 change in colour of the heterogeneous reaction mixture and further ascertained 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.

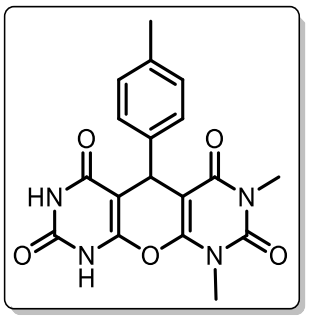
2.2.4 CONCLUSION

In conclusion it can be stated that an efficient methodology for the synthesis of 5-aryl-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraones and 1,3-dimethyl-5-aryl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-triones was developed. The protocol successfully achieved the formation of unsymmetrical pyranodipyrimidines with the aid of $FeCl_3 \cdot 6H_2O$, used as a catalyst. The products formed were isolated through chromatography free method, i.e., by simple filtration, in high purity and the yields obtained were good to excellent. Also, the reaction protocol does not suffer from the formation of any side products despite the presence of highly reactive substrates. The methodology developed is economically viable and environmentally benign. The usage of water as a solvent and $FeCl_3 \cdot 6H_2O$ as a catalyst makes the reaction route greener. Additionally, factors like atom economy, pot economy, usage of less hazardous reactants and safe operational procedure confines it to the boundaries set by the principles of green chemistry.

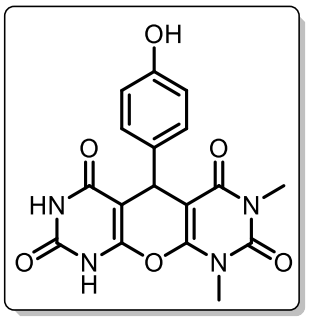
2.2.5 CHARACTERISATION DATA OF THE PRODUCTS



5-(4-(dimethylamino)phenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4aa) Pale yellow solid (364.10 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.12 (s, 1H), 11.05 (s, 1H), 7.35 – 7.22 (m, 2H), 6.71 – 6.65 (m, 2H), 4.86 (s, 1H), 3.93 (s, 3H), 3.85 (s, 3H), 2.91 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 168.6, 167.7, 165.8, 164.4, 151.8, 150.4, 144.4, 129.4, 126.9, 114.0, 109.3, 93.8, 54.3, 44.0, 32.7, 30.1. **HRMS (+ESI)** calcd. for $C_{19}H_{19}N_5O_5$ $(M+H)^+$: 383.1386, found: 383.1389

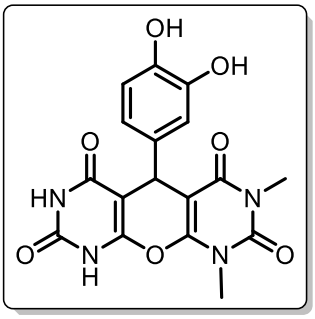


1,3-dimethyl-5-(*p*-tolyl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ab) Pale yellow solid (348.96 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.42 (s, 1H), 10.86 (s, 1H), 8.21 – 8.16 (m, 2H), 7.59 – 7.51 (m, 2H), 5.02 (s, 1H), 3.16 (s, 3H), 2.89 (s, 3H), 2.35 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 172.6, 170.3, 165.9, 161.3, 154.4, 150.3, 144.9, 139.9, 132.0, 129.1, 101.3, 98.8, 56.1, 36.9, 32.7, 24.1. **HRMS (+ESI)** calcd. for $C_{18}H_{16}N_4O_5$ $(M+H)^+$: 368.1121 found: 368.1129

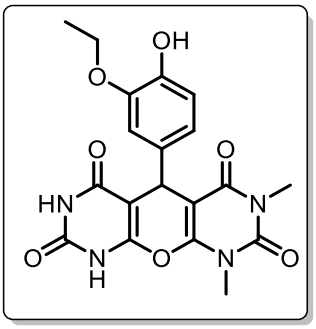


1,3-dimethyl-5-phenyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ac) Pale yellow solid (340.43 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.23 (s, 1H), 11.15 (s, 1H), 7.35 – 7.25 (m, 2H), 6.82 – 6.72 (m, 2H), 5.84 (s, br, 1H), 4.54 (s, 1H), 3.35 (s, 3H), 2.98 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 169.7, 168.3, 165.2, 163.8, 152.4, 145.4, 143.1, 128.3, 127.5, 117.3, 105.0, 95.8, 52.1, 35.1, 32.5. **HRMS (+ESI)**

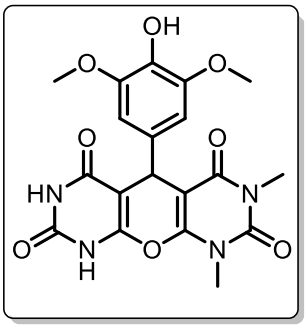
calcd. for $C_{17}H_{14}N_4O_6$ $(M+H)^+$: 370.0913, found: 370.0929



5-(3,4-dihydroxyphenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ad) Deep yellow solid (340.01 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.98 (s, 1H), 10.56 (s, 1H), 8.12 (s, br, 1H), 7.95 (s, 1H), 7.72 (s, br, 1H), 7.60 (d, *J* = 8.4 Hz, 2H), 5.49 (s, 1H), 3.66 (s, 3H), 3.44 (s, 3H).**^{13}C NMR** (100 MHz, DMSO-D_6) δ 171.6, 168.3, 165.7, 158.6, 149.4, 145.2, 144.6, 144.1, 128.6, 120.4, 116.6, 115.7, 103.3, 92.0, 51.8, 30.9, 28.6. **HRMS (+ESI)** calcd. for $C_{17}H_{14}N_4O_7$ $(M+H)^+$: 386.3200 found: 386.3184

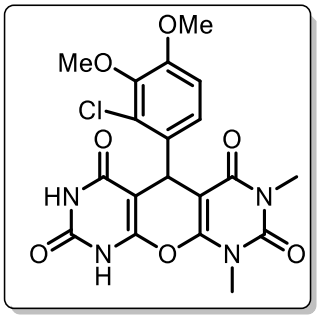


5-(3-ethoxy-4-hydroxyphenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ae) Yellow solid (356.04 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.18 (s, 1H), 10.48 (s, 1H) 7.14 (s, 1H), 6.75 (d, *J*= 7.8 Hz, 1H), 6.74 (d, *J*= 7.8 Hz, 1H), 5.18 (s, 1H), 4.28 (s, br, 1H), 4.16 – 3.91 (m, 2H), 3.23 (s, 3H), 3.15 (s, 3H), 1.47 (t, *J*= 6.1 Hz, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 167.6, 165.3, 160.7, 158.3, 148.4, 144.8, 141.6, 138.1, 128.3, 122.5, 118.6, 115.3, 101.0, 91.8, 62.5, 53.7, 33.9, 30.7, 15.8. **HRMS (+ESI)** calcd. for $C_{19}H_{18}N_4O_7$ $(M+H)^+$: 414.1175, found: 414.1177

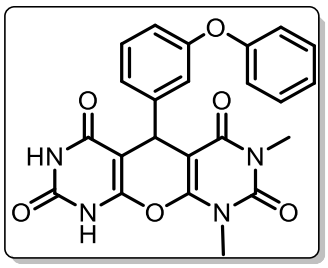


5-(4-hydroxy-3,5-dimethoxyphenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4af) Yellow solid (360.95 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.67 (s, 1H), 10.22 (s, 1H), 7.82 (s, 1H), 6.67 (s, 1H), 6.63 (s, 1H), 5.50 (s, 1H), 3.76 (s, 3H), 3.19 (s, 3H), 2.99 (s, 3H), 2.92 (s, 3H).

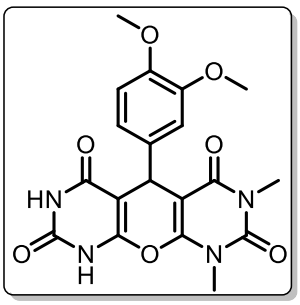
^{13}C NMR (100 MHz, DMSO-*D*$_6$) δ 168.6, 166.3, 158.7, 154.3, 152.4, 150.4, 148.1, 142.1, 135.1, 111.37, 105.0, 98.0, 59.8, 55.2, 36.4, 32.7. **HRMS (+ESI)** calcd. for $C_{19}H_{18}N_4O_8$ $(M+H)^+$: 430.1125 found: 430.1133



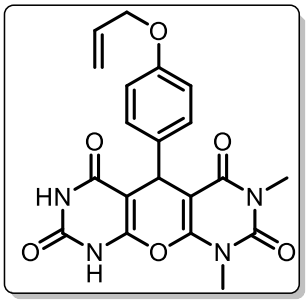
5-(2-chloro-3,4-dimethoxyphenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ag) Yellow solid (376.32 mg) **^{1}H NMR** (400 MHz, DMSO-*D*$_6$) δ 11.22 (s, 1H), 10.83 (s, 1H), 7.53 (s, 1H), 6.91 (s, 1H), 5.48 (s, 1H), 3.68 (s, 3H), 3.53 (s, 3H), 3.06 (s, 3H), 2.88 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-*D*$_6$) δ 165.6, 162.3, 159.9, 155.1, 150.3, 149.0, 143.7, 139.3, 135.7, 129.0, 125.9, 111.3, 105.4, 95.8, 59.6, 56.7, 46.3, 35.4, 31.4. **HRMS (+ESI)** calcd. for $C_{19}H_{17}ClN_4O_7$ $(M+H)^+$: 448.0286, found: 448.0301



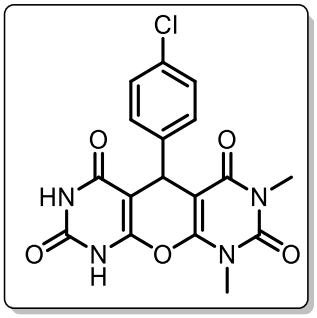
1,3-dimethyl-5-(3-phenoxyphenyl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ah) Orange solid (362.89 mg) **^{1}H NMR** (400 MHz, DMSO-*D*$_6$) δ 10.88 (s, 1H), 10.56 (s, 1H), 7.32 (d, *J* = 7.8 Hz, 2H), 7.27 (s, 1H), 7.18 – 7.11 (m, 2H), 7.02 (d, *J* = 8.4 Hz, 2H), 6.85 – 6.73 (m, 2H), 5.48 (s, 1H), 3.14 (s, 3H), 2.93 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-*D*$_6$) δ 168.6, 166.3, 160.3, 159.7, 159.0, 155.6, 153.44, 148.1, 144.6, 133.5, 131.4, 127.3, 123.9, 123.3, 122.0, 120.5, 107.3, 97.8, 55.7, 34.4, 32.7. **HRMS (+ESI)** calcd. for $C_{23}H_{18}N_4O_6$ $(M+H)^+$: 446.1226 found: 446.1235



1,3-dimethyl-5-(3,4,5-trimethoxyphenyl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ai) **^{1}H NMR** Yellow solid (351.98 mg) (400 MHz, DMSO-D_6) δ 11.01 (s, 1H). 10.65 (s, 1H), 7.15-7.10 (m, 3H), 4.09 (s, 1H), 3.53 (s, 3H), 3.34 (s, 3H), 3.25 (s, 3H), 3.05 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 165.4, 163.1, 162.2, 161.4, 153.1, 151.4, 148.8, 146.2, 139.9, 121.6, 117.6, 110.1, 82.6, 81.4, 56.1, 56.0, 34.6, 31.2, 28.4. **HRMS (+ESI)** calcd. for $C_{19}H_{18}N_4O_7$ $(M+H)^+$: 414.1175 found: 414.1183

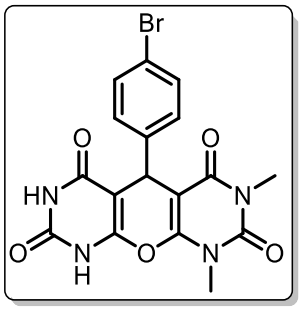


5-(4-(allyloxy)phenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4aj) White solid (356.79 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.14 (s, 1H), 10.96 (s, 1H), 7.29 – 7.15 (m, 4H), 5.34 (d, J = 3.8 Hz, 1H), 5.05 (d, J = 3.4 Hz, 2H), 4.48 (d, J = 4.2 Hz, 1H), 4.39 (s, 1H), 3.05 (s, 3H), 2.88 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 168.5, 167.3, 166.8, 164.7, 152.3, 150.4, 146.1, 136.4, 134.9, 131.5, 119.5, 117.5, 106.0, 94.8, 73.0, 54.1, 32.4, 30.7. **HRMS (+ESI)** calcd. for $C_{20}H_{18}N_4O_6$ $(M+H)^+$: 410.1226, found: 410.1238

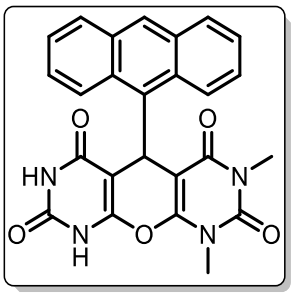


5-(4-chlorophenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ak) White solid (349.21 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.96 (s, 1H), 10.56 (s, 1H), 7.16 – 7.04 (m, 4H), 5.23 (s, 1H), 3.26 (s, 3H), 2.98 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 168.6, 165.3, 163.7, 159.8, 148.7, 142.6, 138.5, 129.5, 124.3, 121.2, 98.3, 88.8, 46.1, 33.4, 31.5. **HRMS (+ESI)** calcd. for $C_{17}H_{13}ClN_4O_5$ $(M+H)^+$:

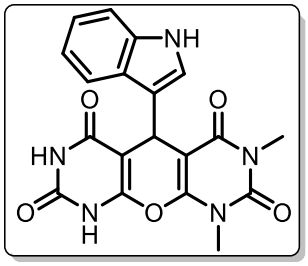
388.0574, found: 388.0591



5-(4-bromophenyl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4al) White solid (388.95 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.97 (s, 1H), 10.88 (s, 1H), 7.48 (d, *J*= 8.4 Hz, 2H), 7.37 (d, *J*= 8.2 Hz, 2H), 5.49 (s, 1H), 3.11 (s, 3H), 2.92 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 164.6, 162.3, 155.7, 151.3, 149.4, 144.1, 138.5, 132.3, 129.7, 124.0, 103.0, 92.8, 50.1, 30.4, 28.7. **HRMS (+ESI)** calcd. for $C_{17}H_{13}BrN_4O_5$ $(M+H)^+$: 432.0069 found: 432.0078

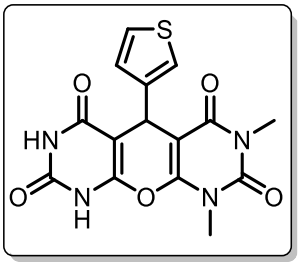


5-(anthracen-9-yl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4am) Dark red solid (354.22 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.11 (s, 1H), 10.78 (s, 1H), 8.56 (s, 1H), 8.12 – 7.99 (m, 2H), 7.89 – 7.77 (m, 2H), 7.57 – 7.50 (m, 4H), 5.67 (s, 1H), 3.46 (s, 3H), 3.12 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 170.6, 168.2, 167.7, 163.8, 154.0, 152.8, 141.4, 139.2, 134.1, 132.7, 131.2, 129.9, 126.7, 108.0, 100.7, 65.3, 34.4, 31.7. **HRMS (+ESI)** calcd. for $C_{25}H_{18}N_4O_5$ $(M+H)^+$: 454.1277, found: 454.1283

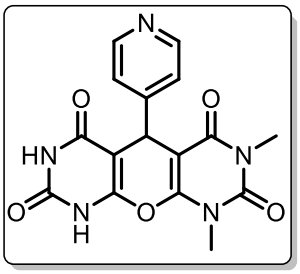


5-(1*H*-indol-3-yl)-1,3-dimethyl-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4an) Brown solid (321.44 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.19 (s, 1H), 11.04 (s, 1H), 9.27 (s, 1H), 7.24 (d, *J* = 6.7 Hz, 2H), 7.16 - 7.08 (m, 2H), 6.77 (d, *J* = 6.8 Hz, 1H), 5.10 (s, 1H), 3.27 (s, 3H), 2.98 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 168.4, 166.2, 163.1, 162.4, 143.5, 137.4, 134.5, 129.1, 125.8, 122.6, 119.3

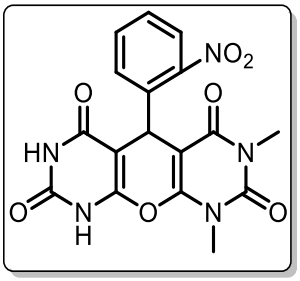
115.5, 111.9, 109.7, 97.5, 38.3, 33.5, 29.8. **HRMS (+ESI)** calcd. for $C_{19}H_{15}N_5O_5$ $(M+H)^+$: 393.1073, found: 393.1085



1,3-dimethyl-5-(thiophen-3-yl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ao) White solid (309.81 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.25 (s, 1H), 11.01 (s, 1H), 7.14 (d, *J*= 7.6 Hz, 1H), 6.96 (d, *J*= 7.4 Hz, 1H), 6.71 (s, 1H), 5.42 (s, 1H), 3.23 (s, 3H), 3.10 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 164.7, 163.3, 155.7, 151.3, 150.5, 141.5, 135.7, 132.3, 125.3, 119.4, 110.6, 95.2, 40.6, 30.4, 28.7. **HRMS (+ESI)** calcd. for $C_{15}H_{12}N_4O_5S$ $(M+H)^+$: 360.0528 found: 360.0529

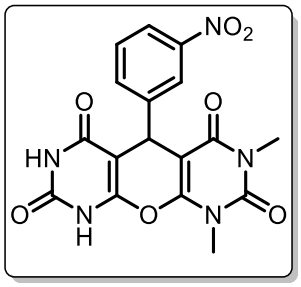


1,3-dimethyl-5-(pyridin-4-yl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ap) White solid (304.98 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.01 (s, 1H), 10.76 (s, 1H), 8.61 – 8.47 (m, 4H), 5.52 (s, 1H), 3.23 (s, 3H), 2.88 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 168.6, 165.2, 154.9, 152.4, 149.4, 148.1, 146.1, 127.5, 108.0, 97.8, 55.1, 31.4, 29.6. **HRMS (+ESI)** calcd. for $C_{16}H_{13}N_5O_5$ $(M+H)^+$: 355.0917 found: 355.0930

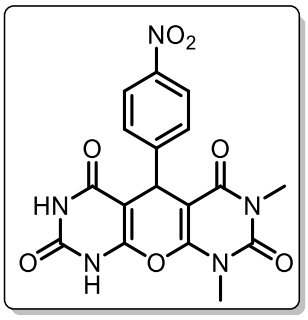


1,3-dimethyl-5-(2-nitrophenyl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4aq) Yellow solid (319.26 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.98 (s, 1H), 8.06 – 7.96 (m, 4H), 5.45 (s, 1H), 3.26 (s, 3H), 2.93 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 164.6, 162.2, 155.9, 151.6, 149.5, 148.0, 144.3, 134.5, 131.2, 130.5, 123.2, 102.9, 92.2, 47.1, 30.4, 28.6. **HRMS (+ESI)** calcd. for $C_{17}H_{13}N_5O_7$

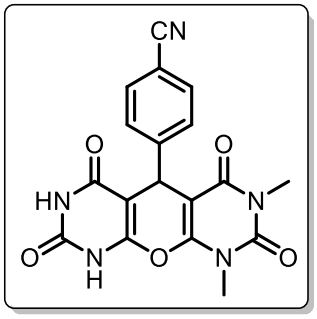
$(M+H)^+$: 399.0815 found: 399.0826



1,3-dimethyl-5-(3-nitrophenyl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4ar) Yellow solid (322.38 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.47 (s, 1H), 11.14 (s, 1H), 8.10 (d, *J* = 5.4 Hz, 1H), 7.82 (s, 1H), 7.54 – 7.48 (m, 2H), 5.32 (s, 1H), 3.23 (s, 3H), 3.12 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 168.9, 166.9, 165.7, 163.4, 149.5, 147.2, 141.2, 136.4, 133.1, 127.4, 122.9, 121.1, 100.2, 96.8, 54.7, 34.3, 32.1. **HRMS (+ESI)** calcd. for $C_{17}H_{13}N_5O_7$ $(M+H)^+$: 399.0815, found: 399.0827

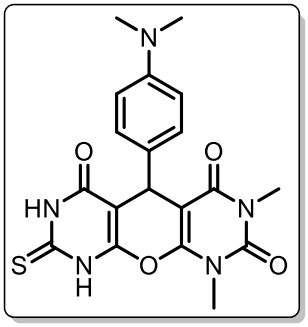


1,3-dimethyl-5-(4-nitrophenyl)-5,9-dihydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6,8(1*H*,3*H*,7*H*)-tetraone (4as)) Yellow solid (339.26 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.10 (s, 1H), 11.05 (s, 1H), 8.62 (d, *J*= 8.4 Hz, 2H), 7.53 (d, *J*= 8.4 Hz, 2H), 5.28 (s, 1H), 3.53 (s, 3H), 3.12 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 170.1, 169.3, 164.5, 158.7, 153.9, 152.2, 149.4, 128.6, 88.8, 82.0, 46.7, 35.8, 33.2. **HRMS (+ESI)** calcd. for $C_{17}H_{13}N_5O_7$ $(M+H)^+$: 399.0815, found: 399.0821

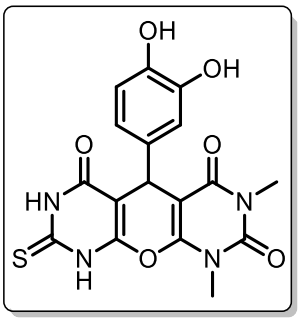


4-(1,3-dimethyl-2,4,6,8-tetraoxo-1,3,4,5,6,7,8,9-octahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidin-5-yl)benzonitrile (4at) White solid (322.13 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.98 (s, 1H), 10.74 (s, 1H), 7.99 – 7.85 (m, 4H), 5.28 (s, 1H), 3.37 (s, 3H), 3.23 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 167.2, 165.7, 161.7, 155.3, 151.4, 149.5, 145.1, 134.3, 131.1, 121.1, 117.6, 105.0, 94.8, 52.1, 36.9, 27.6. **HRMS (+ESI)** calcd. for

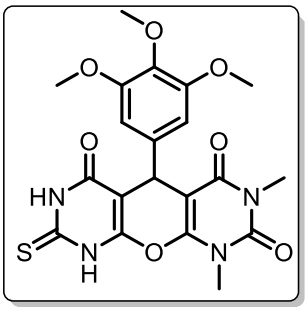
$C_{18}H_{13}N_5O_5$ $(M+H)^+$: 379.0917, found: 379.0936



5-(4-(dimethylamino)phenyl)-1,3-dimethyl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (4ba) Pink solid (367.17 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 11.25 (s, 1H), 11.14 (s, 1H), 7.10 – 6.96 (m, 4H), 5.47 (s, 1H), 3.99 (s, 3H), 3.76 (s, 3H), 3.08 (s, 6H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 178.6, 168.3, 162.9, 159.6, 155.8, 152.9, 148.1, 133.10, 131.5, 127.9, 126.7, 103.1, 98.7, 54.8, 33.7, 31.7. **HRMS (+ESI)** calcd. for $C_{18}H_{17}N_5O_4S$ $(M+H)^+$: 399.1001, found: 399.1013

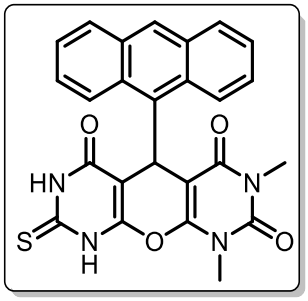


5-(3,4-dihydroxyphenyl)-1,3-dimethyl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (4bb) Deep yellow solid (341.78 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.78 (s, 1H), 10.61 (s, 1H), 8.63 (s, 1H), 6.98 – 6.88 (m, 2H), 6.02 (s, br, 1H), 5.67 (s, br, 1H), 5.21 (s, 1H), 3.26 (s, 3H), 2.97 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 180.4, 168.3, 163.5, 155.7, 152.2, 145.2, 144.6, 144.3, 128.9, 120.4, 116.6, 115.8, 103.3, 95.1, 51.7, 31.4, 29.6. **HRMS (+ESI)** calcd. for $C_{17}H_{14}N_4O_6S$ $(M+H)^+$: 402.0634 found: 402.0639

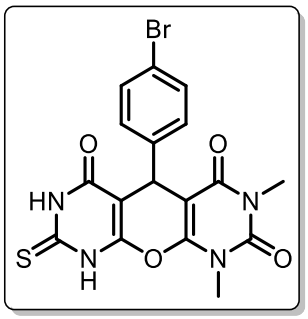


1,3-dimethyl-8-thioxo-5-(3,4,5-trimethoxyphenyl)-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (4bc) Yellow solid (386.41 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.98 (s, 1H), 10.72 (s, 1H), 8.64 (s, 1H), 8.23 (s, 1H), 5.13 (s, 1H), 3.76 (s, 3H), 3.62 (s, 3H), 3.59 (s, 3H), 3.15 (s, 3H), 2.78 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 180.4, 172.3,

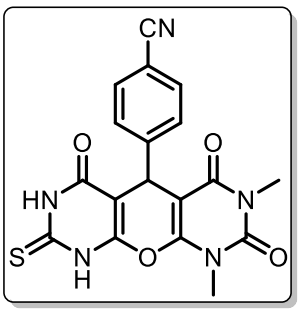
169.5, 165.9, 152.2, 151.9, 144.3, 141.8, 131.3, 108.5, 103.3, 95.6, 60.6, 56.5, 51.2, 37.9, 33.6. **HRMS (+ESI)** calcd. for $C_{20}H_{20}N_4O_7S$ $(M+H)^+$: 460.1053 found: 460.1066



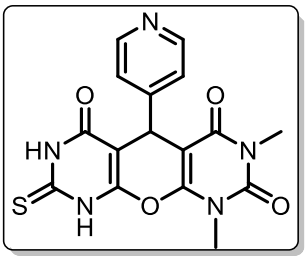
5-(anthracen-9-yl)-1,3-dimethyl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (4bd) Dark red solid (357.20 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.67 (s, 1H), 10.57 (s, 1H), 8.41 (s, 1H), 8.10 – 7.90 (m, 2H), 7.90 – 7.77 (m, 2H), 7.59 – 7.52 (m, 4H), 4.81 (s, 1H), 3.41 (s, 3H), 3.12 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 176.4, 164.3, 157.6, 152.2, 141.7, 139.2, 133.4, 127.6, 125.8, 124.9, 124.7, 123.1, 122.3, 101.4, 93.2, 56.4, 29.8, 25.6. **HRMS (+ESI)** calcd. for $C_{25}H_{18}N_4O_4S$ $(M+H)^+$: 470.1049, found: 470.1058



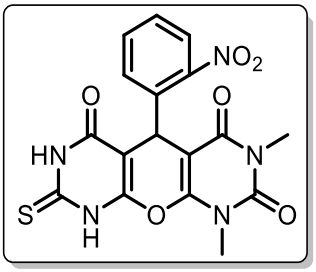
5-(4-bromophenyl)-1,3-dimethyl-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (4be) White solid (394.31 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 8.64 (s, 1H), 7.50 – 7.35 (m, 2H), 7.35 – 7.21 (m, 2H), 4.50 (s, 1H), 3.15 (m, 3H), 2.92 (m, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.4, 162.3, 159.5, 155.7, 152.2, 144.3, 138.5, 132.0, 129.8, 124.0, 103.0, 95.1, 50.1, 30.4, 28.7. **HRMS (+ESI)** calcd. for $C_{17}H_{13}BrN_4O_4S$ $(M+H)^+$: 447.9841 found: 447.9859



4-(1,3-dimethyl-2,4,6-trioxo-8-thioxo-1,3,4,5,6,7,8,9-octahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidin-5-yl)benzonitrile (4bf) White solid (335.89 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.66 (s, 1H), 10.12 (s, 1H), 8.19 – 8.04 (m, 4H), 5.43 (s, 1H), 3.15 (s, 3H), 2.92 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 183.4, 174.2, 169.0, 165.7, 162.2, 156.5, 148.1, 138.6, 132.1, 122.2, 118.8, 103.3, 96.6, 54.3, 36.9, 32.7. **HRMS (+ESI)** calcd. for $C_{18}H_{13}N_5O_4S$ $(M+H)^+$: 395.0688 found: 395.0692



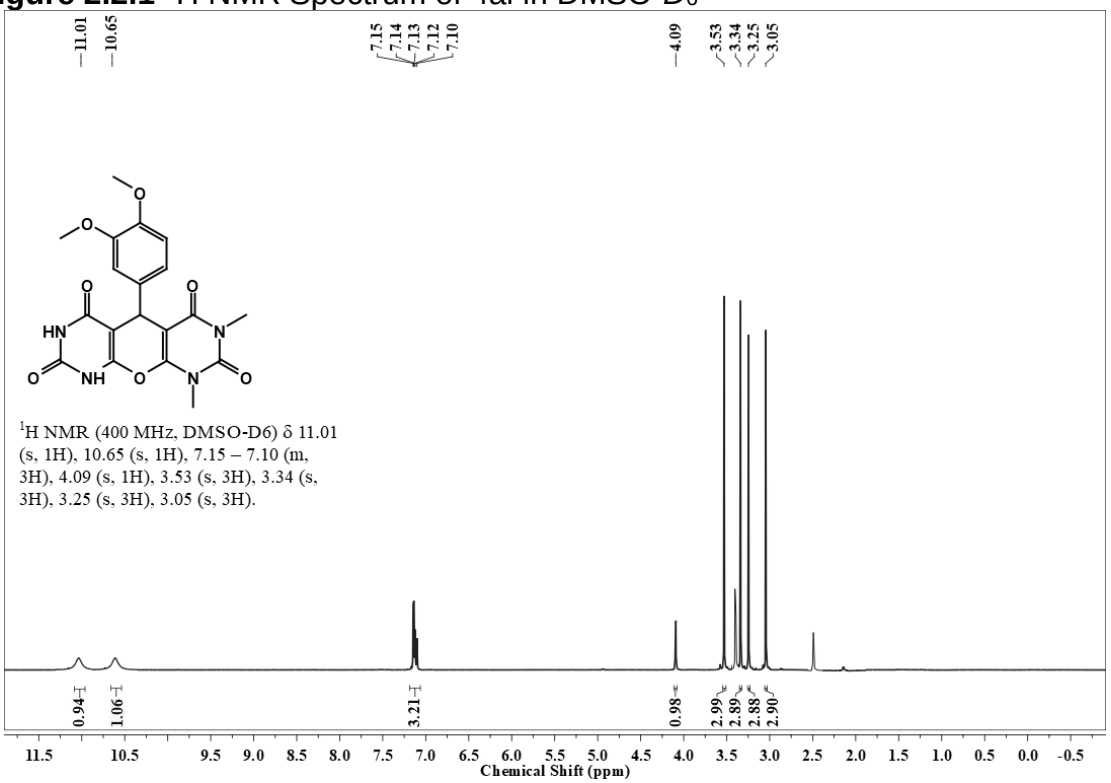
1,3-dimethyl-5-(pyridin-4-yl)-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (4bg) White solid (319.15 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.92 (s, 1H), 10.64 (s, 1H) 8.59 (d, *J*= 8.2 Hz, 2H), 7.27 (d, *J*= 8.2 Hz, 2H), 5.54 (s, 1H), 3.45 (s, 3H), 3.22 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 182.4, 175.3, 168.5, 165.9, 155.2, 150.2, 148.1, 125.2, 105.0, 98.6, 52.1, 33.4, 29.6. **HRMS (+ESI)** calcd. for $C_{16}H_{13}N_5O_4S$ $(M+H)^+$: 371.0688 found: 371.0697



1,3-dimethyl-5-(2-nitrophenyl)-8-thioxo-5,7,8,9-tetrahydro-2*H*-pyrano[2,3-*d*:6,5-*d*']dipyrimidine-2,4,6(1*H*,3*H*)-trione (4bh) Yellow solid (340.26 mg) **^{1}H NMR** (400 MHz, DMSO-D_6) δ 10.64 (s, 1H), 10.29 (s, 1H), 8.02-7.77 (m, 4H), 5.57 (s, 1H), 3.54 (s, 3H), 3.07 (s, 3H). **^{13}C NMR** (100 MHz, DMSO-D_6) δ 179.4, 165.3, 163.5, 155.9, 151.3, 147.7, 145.7, 131.5, 130.2, 128.7, 125.2, 98.9, 92.1, 52.1, 33.4, 29.7. **HRMS (+ESI)** calcd. for $C_{17}H_{13}N_5O_6S$ $(M+H)^+$: 415.0587 found: 415.0601

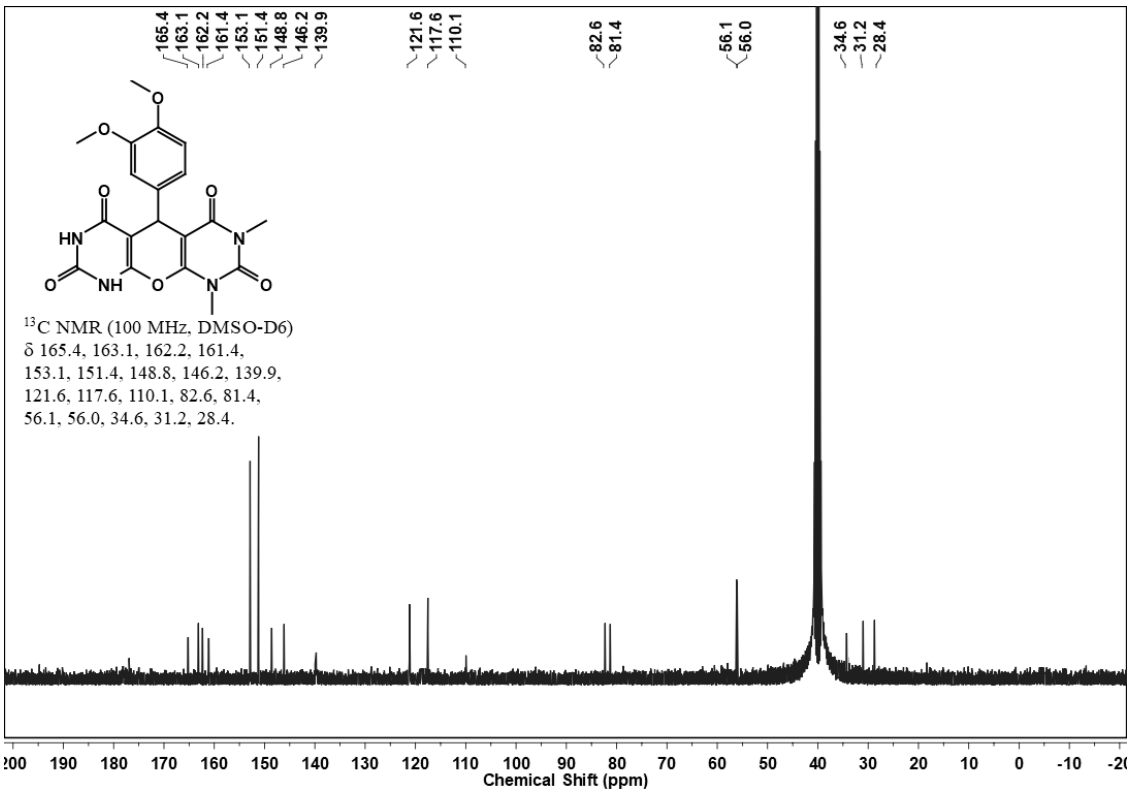
2.2.6 REPRESENTATIVE NMR SPECTRA

Figure 2.2.1 ^{1}H NMR Spectrum of 4ai in DMSO-D_6



^{1}H NMR (400 MHz, DMSO-D6) δ 11.01 (s, 1H), 10.65 (s, 1H), 7.15 – 7.10 (m, 3H), 4.09 (s, 1H), 3.53 (s, 3H), 3.34 (s, 3H), 3.25 (s, 3H), 3.05 (s, 3H).

Figure 2.2.2 ^{13}C NMR Spectrum of 4ai in DMSO-D_6



^{13}C NMR (100 MHz, DMSO-D6) δ 165.4, 163.1, 162.2, 161.4, 153.1, 151.4, 148.8, 146.2, 139.9, 121.6, 117.6, 110.1, 82.6, 81.4, 56.1, 56.0, 34.6, 31.2, 28.4.

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