5.1 Introduction

The primary emphasis in C-C/C-X bond-forming reactions has shifted towards the formation of carbon-carbon (C-C) and carbon-heteroatom (C-X) bonds through oxidative transformation, thereby eliminating the need for prefunctionalized substrates and reducing the production of salt waste. This approach promotes enhanced sustainability and environmental compatibility.[1–3] The increasing utilization and interest in direct oxidative C-H functionalization over the past two decades demonstrate this sustainable synthetic technology's significance and growing importance.[4,5] Potassium persulfate ($K_2S_2O_8$ is an affordable and easily accessible inorganic oxidant) has demonstrated exceptional compatibility with a broad range of oxidative transformations, encompassing both inorganic and organic oxidants. Its versatility extends from academic laboratories to industrial processes.[6–8]

Nitrogen-containing heterocycles are found as subunits in a wide variety of natural products and pharmaceuticals. Among these, 1,4-dihydropyridine[9] substructures frequently occur, with felodipine, israpidine, and NADPH being the most notable (**Figure 5.1**). Additionally, they are especially versatile building blocks, making them especially suitable for forming piperidines, among the most common heterocyclic targets in pharmaceuticals and agrochemicals.

There has been an increase in medicinal and organic chemistry use for pyrido[2,3-d]pyrimidine derivatives among 1,4-dihydropyridine derivatives. Because pyrido[2,3-

d]pyrimidines exhibit high biological activity, a number of multicomponent reactions have been reported in the past decade. These synthetic methods suffered from some limitations, mainly including harsh reaction conditions, low reaction efficiency, toxic solvent, restricted reactants, etc. (**Scheme 5.1a**). As a result, there has been considerable interest in organic synthesis towards enhancing and upgrading these reactions. However, the vast majority of these type of reactions were achieved by using aldehydes as the C4 source of pyrido[2,3-d]pyrimidines, and catalyzed or promoted by using glycerol[10], an electrolytic reaction in ethanol[11], tetrabutyl ammonium bromide (TBAB)[12], diammonium hydrogen phosphate (DAHP)[13], sulfonic acid functionalized SBA-15 (SBA-Pr-SO_3H)[14], triethylbenzylammonium chloride (TEBAC)[15], Fe_3O_4@SiO_2-supported ionic liquid nanocatalyst,[16] Al-HMS-20,[17] triethylamine (TEA) in aqueous ethanol,[18] Lewis base surfactantcombined catalyst (LBSC),[19] $CuFe_2O_4$ nanoparticles in water[20], $Zr(HSO_4)_4$ nanoparticles[21], nanocrystalline MgO in water[22], Fe_3O_4–ZnO–NH_2–$PW_{12}O_{40}$ nanocatalyst[23], and Magnetic Fe_3O_4-TiO_2-NH_2-$PMo_{12}O_{40}$ Nanoparticles[24] to access a wide range of diversified pyrido[2,3-d]pyrimidines derivatives. (**Scheme 5.1b**)

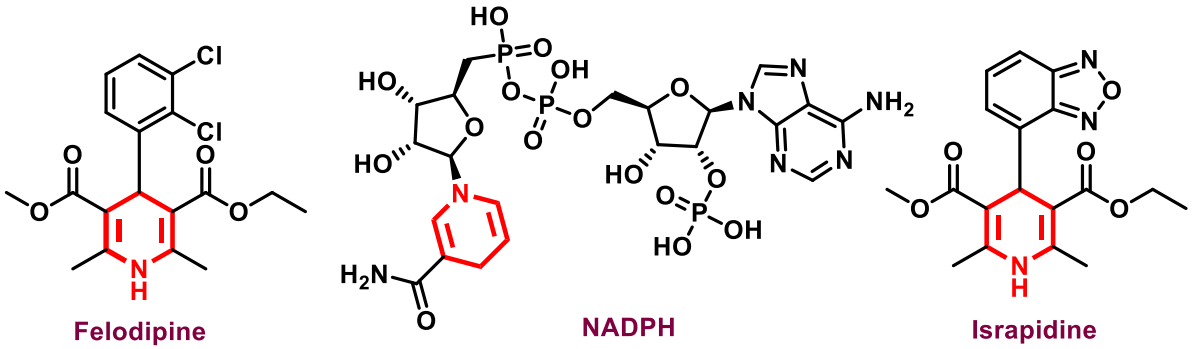
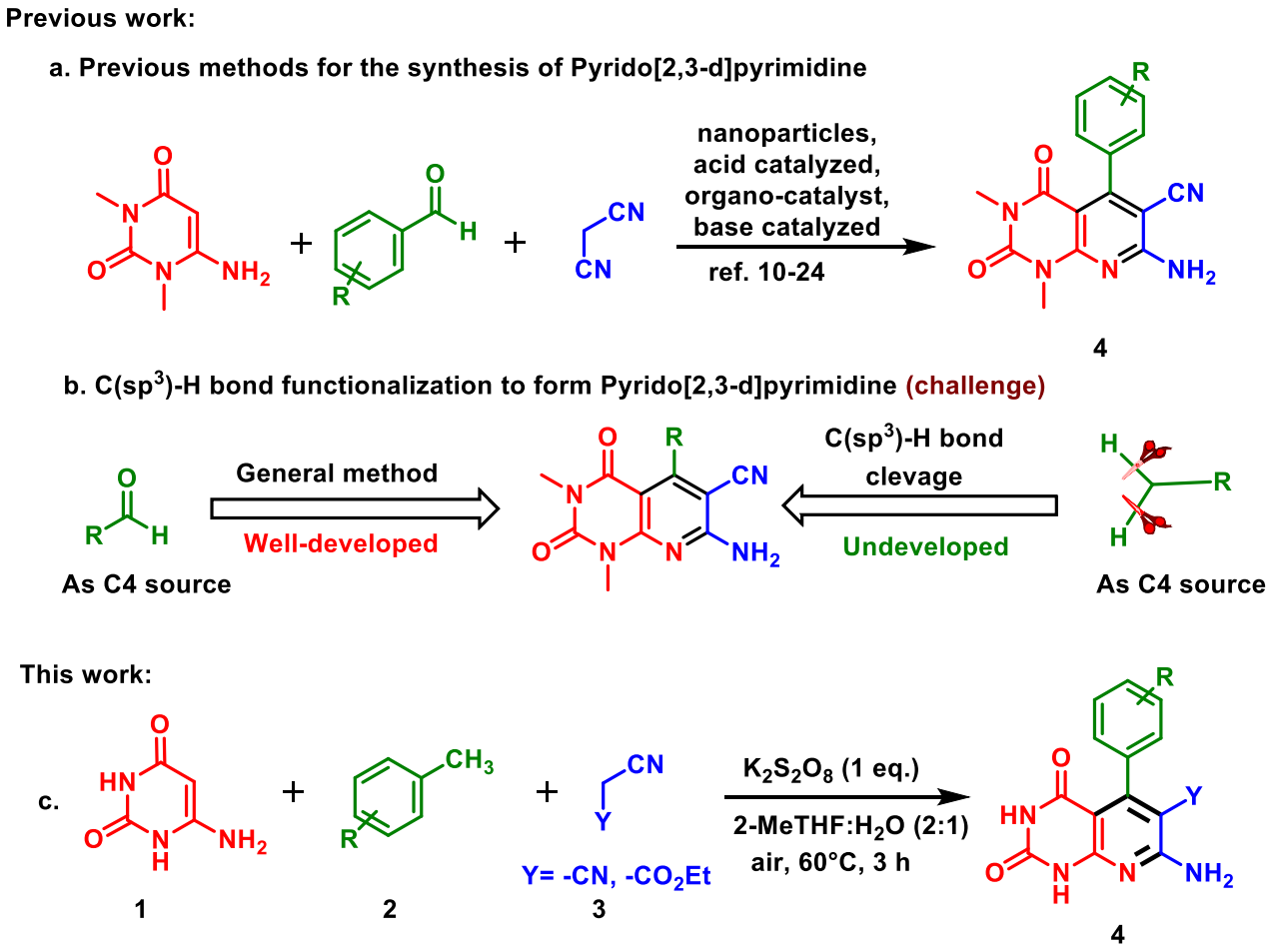


Figure 5.1 Most representative biologically active 1,4-dihydropyridines

On the other hand, using readily available and abundant C(sp^3)-H bond substrates like methyl arenes, alkyl amines, ethers, alcohols, etc., for C(sp^3)-H bond functionalization and C(sp^3)-H cleavage poses challenges due to their higher bond energy and inertness. Despite well-established methods, the construction of Pyrido[2,3-d]pyrimidines using C(sp^3)-H bond substrates as the C4 source remains difficult. Notably, the synthesis of Pyrido[2,3-d]pyrimidines utilizing methyl arene as the C4 source has yet to be documented. (**Scheme 5.1b**)

With our continued interest in green synthetic chemistry[25–30], Herein we demonstrate for the first time an oxidative [3+2+1] cyclization of 6-aminouracil, methyl arenes, and active methylene compound to construct useful substituted Pyrido[2,3-d]pyrimidines. (**Scheme 5.1c**). In this protocol, the new strategy for the construction of Pyrido[2,3-d]pyrimidines by using methyl arene as the C4 source, cheap oxidant as a $K_2S_2O_8$(transition metal-free approach), 2-MeTHF: H_2O (2:1) as a green solvent, and easy operation under an atmospheric air are achieved.



Scheme 5.1 Various procedures for synthesis of Pyrido[2,3-d]pyrimidine

5.2 Results and Discussion

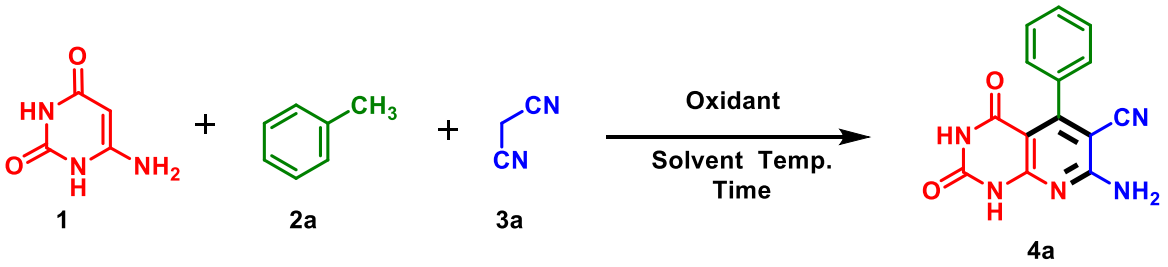
In the context of optimizing conditions (Table 5.1), a reaction was conducted using 6-amino uracil (**1**), toluene (**2a**), and malononitrile (**3a**) as the model substrate. The reaction utilized $K_2S_2O_8$ (1.0 equiv.) as an oxidant and CH_3CN as a solvent, with a temperature of 80°C for a duration of 8 hours. As a result, a 38% yield of the product **(4a)** was achieved (Table 5.1, entry 1). Subsequently, additional solvents were tested, including DMSO, THF, DMF, and 2-MeTHF (entries 2-5), and out of these, 2-Me THF yielded 42% successfully at 60°C in 6

hours. Considering the principles of green synthesis and solubility of reagents, we utilized a reaction solvent consisting of a mixture of 2-MeTHF and water, which resulted in the successful production of the desired product with a high yield at 60°C in 3 hours. Taking into consideration these characteristics, various proportions of the aqueous solvent with 2-MeTHF were investigated, and it was discovered that the mixed solvent (2-MeTHF: H_2O=2:1) was the most favorable choice (Table 5.1, entries 6-9). The structure of the obtained product 4a was confirmed using ^{1}H NMR and ^{13}C NMR. Additionally, we adjusted the $K_2S_2O_8$ loading from 1 mol % to 2 and 3 mol % (Table 5.1, entries 10-11) and observed a decrease in yield as the mol% of the oxidant increased. Afterward, various alternative oxidants were investigated, and the outcomes indicated that $K_2S_2O_8$ played a crucial role in achieving the highest/most favorable yield (Table 5.1, entries 12-16). Significantly, the analysis of oxidant-loading (Table 5.1, entries 12-16) and solvent ratio-loading (Table 5.1, entries 6-9) demonstrated that the use of 1.0 eq. of $K_2S_2O_8$ and a 2:1 ratio of 2-MeTHF: H_2O was found to be compatible with this transformation (Table 5.1, entry 8).

After optimizing the reaction conditions, we assessed the method's applicability by expanding it to different methyl arene and active methyl compounds while maintaining a constant 6-amino uracil. This allowed us to obtain a range of Pyrido[2,3-d]pyrimidine derivatives (**4a–4zf)** with yields ranging from 83% to 93%. (Table 5.2 and 5.3) We were pleased to find that the reaction exhibited compatibility with methyl arene possessing different electron properties and substitution patterns.

At the outset, we explored the influence of substituents on the aromatic ring of the methyl arenes moiety. Under optimized reaction conditions, the incorporation of various substituents such as electron-donating groups (-isopropyl, -tertiary butyl, -OMe), electron-withdrawing groups (-CHO, -NO_2), and halogens (-F, -Cl, and -Br) at the ortho- and para- position of the methyl arenes moiety demonstrated good tolerance and yielded products ranging from 85% to 93% yield with shorter reaction time. The substrates featuring diverse functional groups like nitro, and chloro groups positioned at the meta-position of the phenyl ring exhibited excellent tolerance and were successfully converted into the respective products **(4e, 4h, 4t, and 4x)** with good yields. This reaction system demonstrated compatibility with substrates containing multi-substituted methyl arene, allowing for the smooth formation of the desired products (**4j, 4m, 4y, and 4zb**) with yields ranging from moderate to excellent.

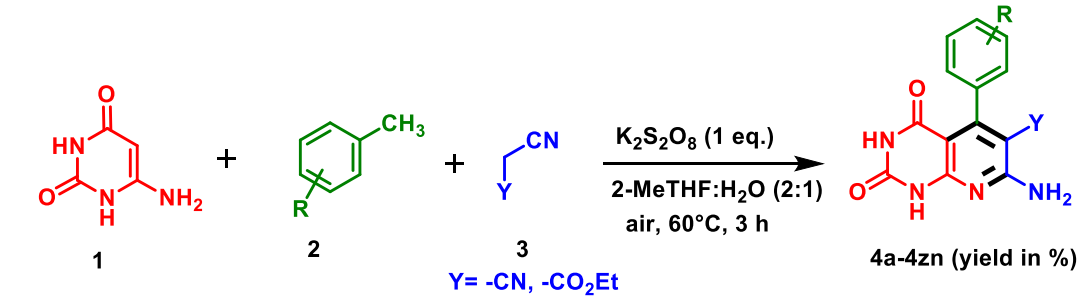
Table 5.1 Optimization of the Reaction Conditions[a]

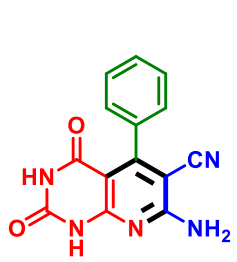


entry	solvent	oxidant (eq.)	T (°C)	time (h)	yield[b] (%)
1	CH_3CN	$K_2S_2O_8$ (1)	80	8	38
2	DMSO	$K_2S_2O_8$ (1)	90	12	trace
3	THF	$K_2S_2O_8$ (1)	60	8	25
4	DMF	$K_2S_2O_8$ (1)	90	12	trace
5	2-MeTHF	$K_2S_2O_8$ (1)	60	6	42
6	2-MeTHF:H_2O (1:1)	$K_2S_2O_8$ (1)	60	5	68
7	2-MeTHF:H_2O (1:2)	$K_2S_2O_8$ (1)	60	6	55
8	2-MeTHF:H_2O (2:1)	$K_2S_2O_8$ (1)	60	3	89
9	2-MeTHF:H_2O (3:1)	$K_2S_2O_8$ (1)	60	3	85
10	2-MeTHF:H_2O (2:1)	$K_2S_2O_8$ (2)	60	4	80
11	2-MeTHF:H_2O (2:1)	$K_2S_2O_8$ (3)	60	4	79
12	2-MeTHF:H_2O (2:1)	$Na_2S_2O_8$ (1)	60	6	75
13	2-MeTHF:H_2O (2:1)	$(NH_4)_2S_2O_8$ (1)	60	6	76
14	2-MeTHF:H_2O (2:1)	TBHP (1)	60	8	55
15	2-MeTHF:H_2O (2:1)	Oxone (1)	60	8	56
16	2-MeTHF:H_2O (2:1)	H_2O_2 (1)	60	8	59

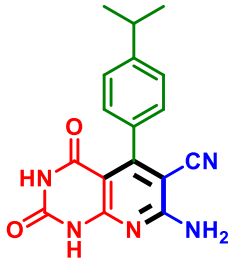
[a]Experimental condition: The reactions were performed using 1 (1 mmol), 2a (1 mmol), 3a (1 mmol), an oxidant, and a solvent (3.0 mL) under air in a 60°C oil bath for 3 h.
[b]Isolated yields after recrystallization from EtOH.

Table 5.2 Three-component reaction of 6-aminouracil with different methyl arene and active methylene compounds

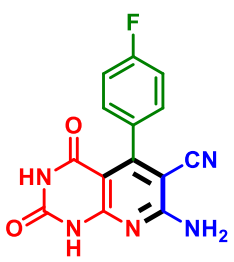




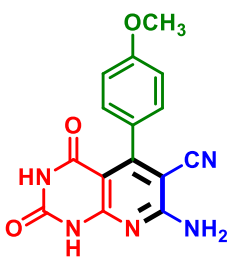
4a (89%)



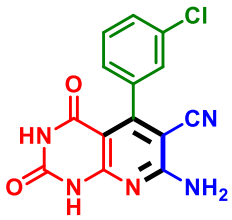
4b (91%)



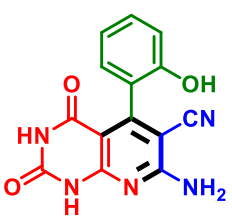
4c (90%)



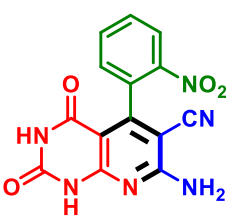
4d (90%)



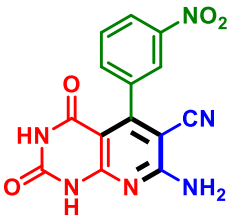
4e (85%)



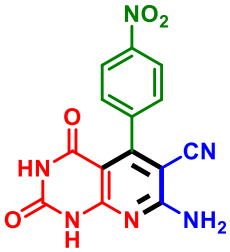
4f (84%)



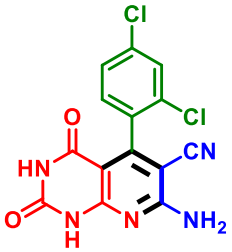
4g (89%)



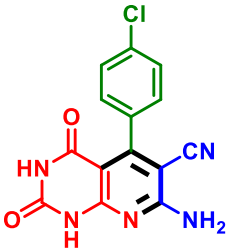
4h (86%)



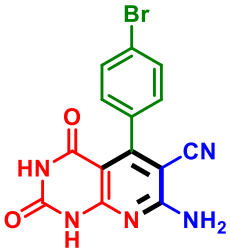
4i (93%)



4j (91%)



4k (89%)



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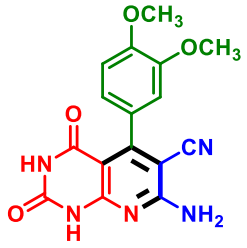
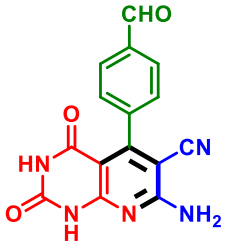


4m (91%)



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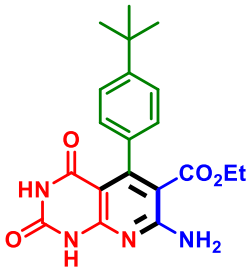
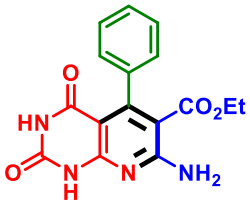
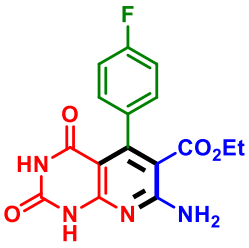


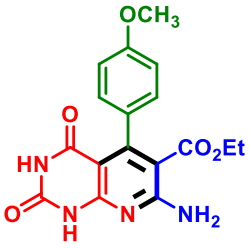
4o (90%)



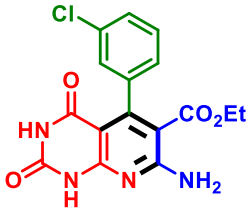
4p (88%)



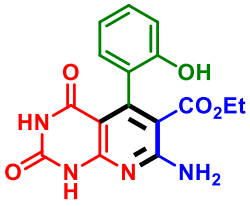
4r (90%)



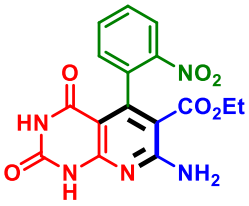
4s (91%)



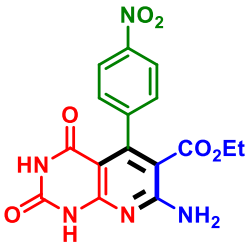
4t (83%)



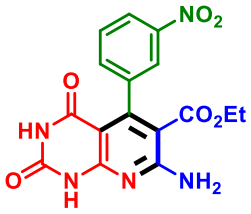
4u (85%)



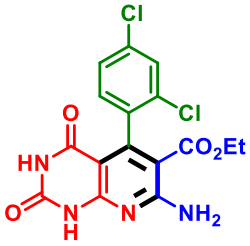
4v (89%)



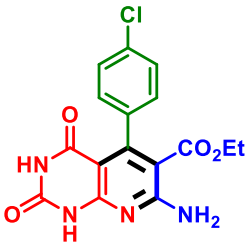
4w (92%)



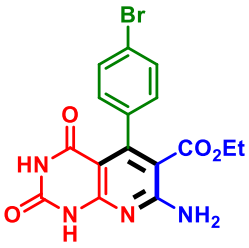
4x (85%)



4y (89%)



4z (88%)



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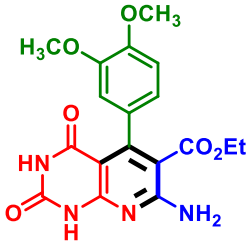

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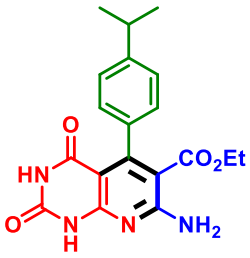

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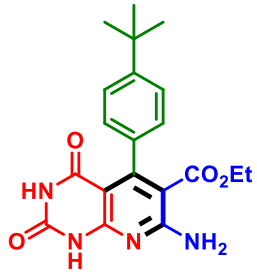

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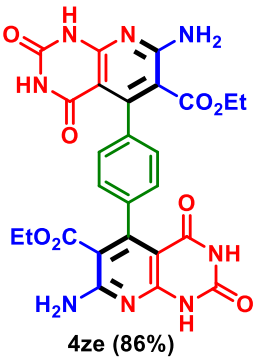
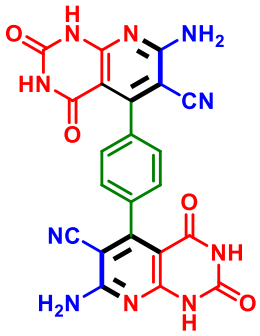


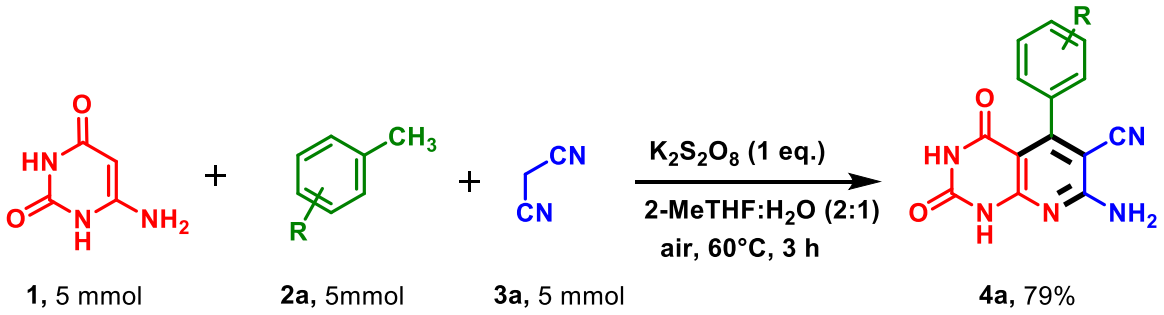
4ze (86%)



4zf (88%)

Experimental condition: The reactions were performed using **1** (1 mmol), **2a** (1 mmol), **3a** (1 mmol), $K_2S_2O_8$ (1 eq), and 2-Me THF: H_2O=2:1 (3.0 mL) under air in a 60°C oil bath for 3 h.

After the optimization of the reaction condition, a large-scale experiment was conducted under standard conditions to assess the practical applicability of this reaction, resulting in the desired product **4a** being obtained with a yield of 79%. **(Scheme 5.2)**



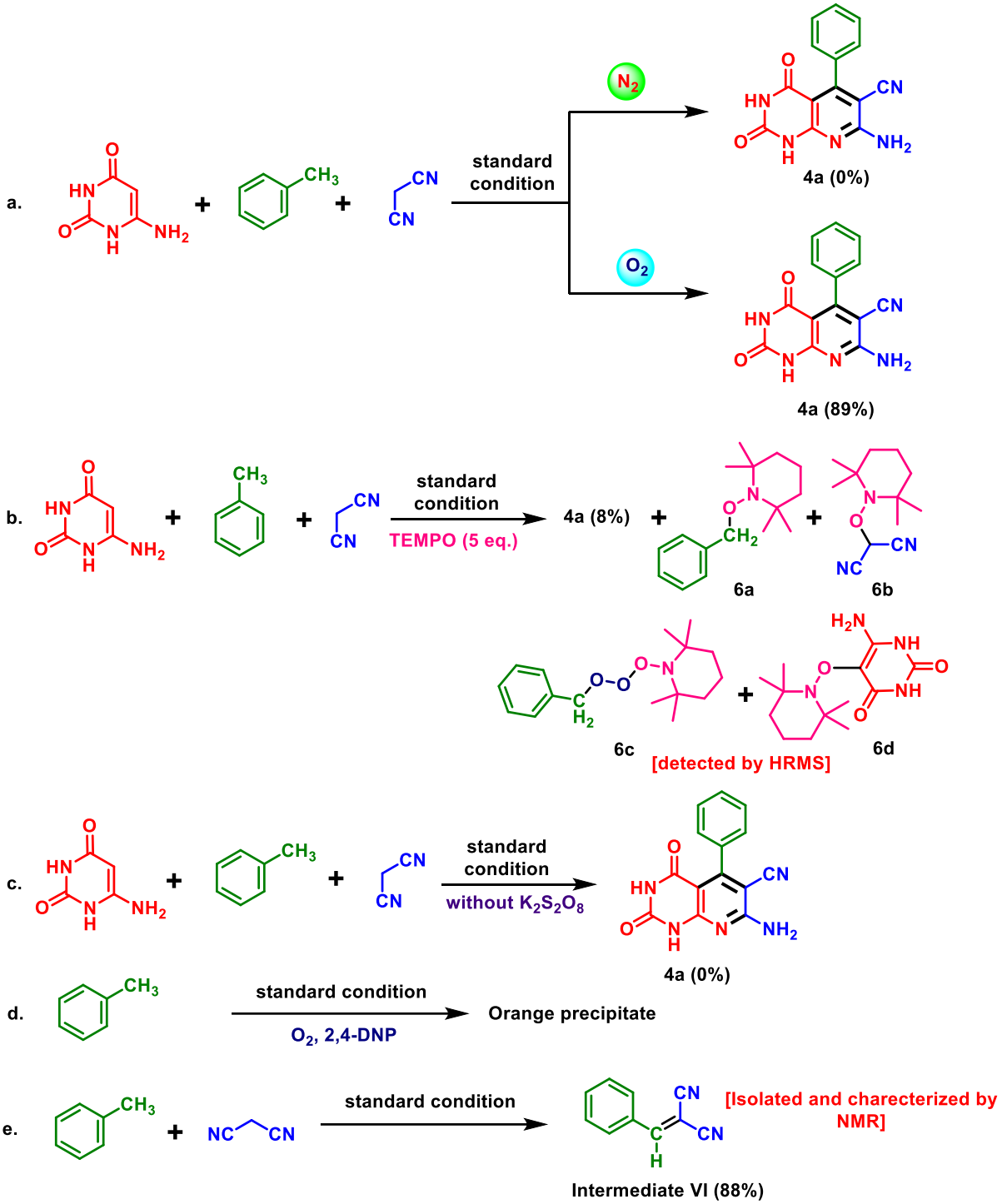
Scheme 5.2 The gram-scale reaction

5.3 Control Experiment

To elucidate the reaction mechanism, several control experiments were conducted. As illustrated in **Scheme 5.3**, the reaction carried out under an N_2 atmosphere (**entry a**) failed to yield the desired product **4a**, demonstrating the essential role of O_2 for the success of the

reaction. Additionally, with the introduction of 5 equivalents of the radical scavenger TEMPO (2,2,6,6-tetramethylpiperidin-1-oxyalkyl), there was a significant reduction in the formation of **4a** (**Scheme 5.3, entry b**). A free radical mechanism was confirmed by identifying adducts **6a**, **6b**, **6c**, and **6d**, which were characterized using HRMS. Next, the reaction without $K_2S_2O_8$ gives no product indicating that the $K_2S_2O_8$ plays an important role in this reaction (**Scheme 5.3, entry c**).

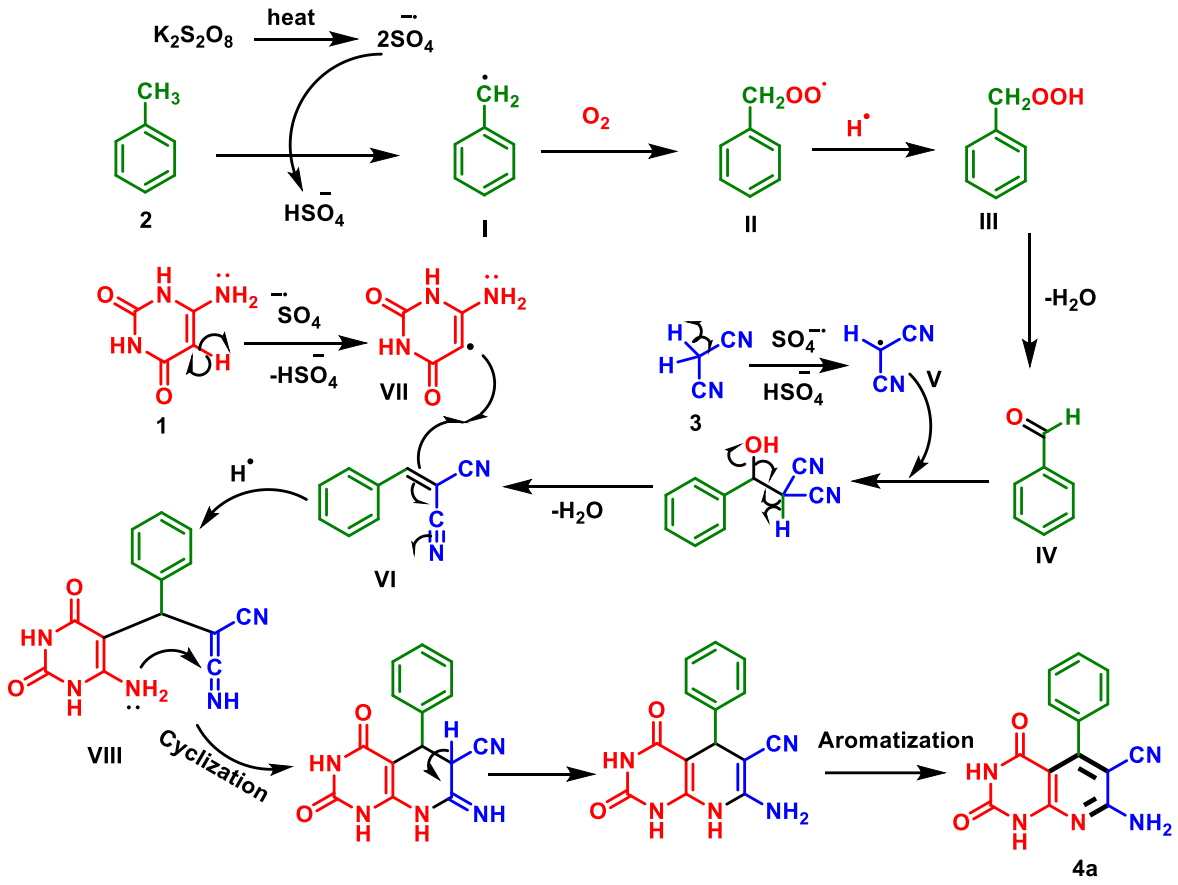
In order to investigate the reaction mechanism, additional control experiments were carried out. The reaction of methyl arenes was conducted under standard conditions in the presence of 2, 4-DNP to confirm the presence of an intermediate. The formation of an orange precipitate confirms the involvement of an aldehyde intermediate (**Scheme 5.3, entry d**). Under standard conditions, the reaction between methyl arenes (**2a**) and malononitrile (**3a**) yielded intermediate **VI** with an 88% yield (**Scheme 5.3, entry e**). The formation of intermediate **VI** was confirmed by characterizing it using ^{1}H and ^{13}C NMR spectroscopy.



Scheme 5.3 Control experiment for mechanistic investigation

5.4 Proposed Mechanism

Scheme 5.4 presents a plausible mechanism based on the experimental findings and previous research[31–33]. First, the thermal decomposition of $K_2S_2O_8$ to form the sulfate radical ($SO4^{-\bullet}$). When the sulfate radical reacts with methyl arenes **2**, benzyl radical (intermediate **I**) is produced. Subsequently, this intermediate is captured by oxygen, generating peroxo-species (intermediate **II**). Subsequent H-radical abstraction converts the peroxo-species into benzyl hydroperoxide (intermediate **III**). Upon the elimination of a water molecule, intermediate **III** undergoes in-situ formation to produce benzaldehyde (intermediate **IV**). The sulfate radical abstract hydrogen radical from **3** to form the malononitrile radical (intermediate **V**), which react with intermediate **IV** to form intermediate **VI** by removing water. Again sulfate radical abstract hydrogen radical from **1** to form intermediate **VII**, and react with intermediate **VI** to form intermediate **VIII**. This intermediate **VIII** undergoes intramolecular cyclization and aromatization to form product **4a**.



Scheme 5.4 Plausible mechanism

5.5 Conclusions

In conclusion, An environmentally friendly and sustainable method has been devised to efficiently produce a range of Pyrido[2,3-d]pyrimidines; the reaction system fulfills the criteria of sustainable chemistry by utilizing transition metal-free green solvents and affordable oxidants. Additionally, it offers the advantage of being performed under ambient air and aqueous conditions, facilitating its scalability for larger-scale experiments. In this procedure, methylarenes are utilized as the C4 source for the Pyrido[2,3-d]pyrimidines framework, leading to the simultaneous formation of one C(sp^3)-C(sp^2) bond, one C(sp^3)-

C(sp^3) bond, and one C(sp)-N(sp^2) bond through the functionalization/cyclization of methylarenes, 6-amino uracil, and active methylene compounds. Through an in-depth mechanistic investigation, it has been shown that the reaction follows a radical mechanism, with the formation of intermediates indicating C–H functionalization.

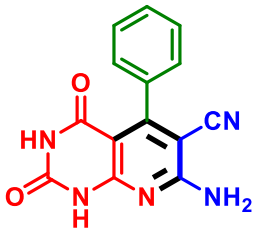
5.6 Experimental Procedures

5.6.1 General procedure for the preparation of compounds 4a-4zf

In a 25 mL round-bottom flask, 6-amino uracil **1** (1 mmol), methyl arenes **2** (1.0 mmol), active methylene compound **3** (1 mmol), $K_2S_2O_8$ (1 mmol, 1 eq), 2-MeTHF (2.0 mL), and water (1.0 mL) were combined. The resulting mixture was stirred at 60°C for 3 hours, and the progress of the reaction was monitored using TLC. Subsequently, the mixture was cooled to room temperature, and EtOAc (15 mL×2) was added. The organic phase was washed with water (10 mL), dried using Na_2SO_4, concentrated, and subjected to column chromatography purification to yield Pyrido[2,3-d]pyrimidine (**4**).

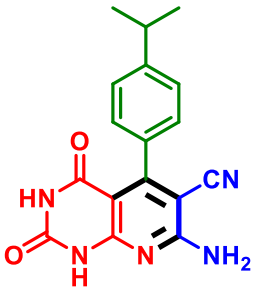
5.7 Characterization of products

7-amino-2,4-dioxo-5-phenyl-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4a)



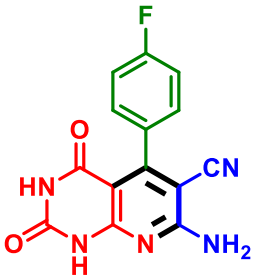
Red solid (89%), mp >300°C, IR (KBr, cm^{-1}): 3617, 3514, 3287, 2220, 1713, 1595. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.51 (s, 1H), 10.31 (s, 1H), 7.48 – 7.35 (m, 1H), 7.28 – 7.16 (m, 2H), 7.14 – 7.02 (m, 2H), 6.72 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 160.48, 159.45, 155.98, 150.28, 139.96, 128.14, 126.99, 125.37, 115.94, 98.61, 89.14. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_9N_5O_2$ 280.0834; found: 280.0837

7-amino-5-(4-isopropylphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4b)



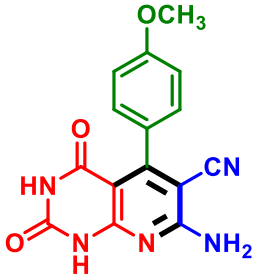
Light yellow solid (91%), mp >300°C, IR (KBr, cm^{-1}): 3610, 3512, 3285, 2215, 1709, 1591. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.53 (s, 1H), 10.21 (s, 1H), 7.95 (d, 2H), 7.53 (d, 2H), 6.52 (s, 2H). 2.91 – 2.85 (m, 1H), 1.21 (d, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 161.48, 158.45, 153.98, 151.30, 148.28, 139.96, 128.14, 126.99, 125.37, 115.94, 98.75, 88.18, 33.21, 23.02. HRMS (ESI) m/z: [M+H] + calculated for $C_{17}H_{15}N_5O_2$ 322.1304; found: 322.1301

7-amino-5-(4-fluorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4c)



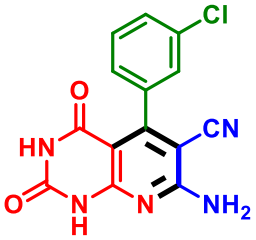
White solid (90%), mp >300°C, IR (KBr, cm^{-1}): 3620, 3518, 3290, 2227, 1721, 1599. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.48 (s, 1H), 10.21 (s, 1H), 7.22 – 7.17 (d, 2H), 7.01 (d, 2H), 6.12 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 165.30, 160.40, 159.46, 159.30, 155.90, 150.28, 139.96, 128.14, 126.99, 125.37, 115.94, 99.51, 86.14. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_8N_5O_2F$ 298.0740; found: 298.0742.

7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4d)



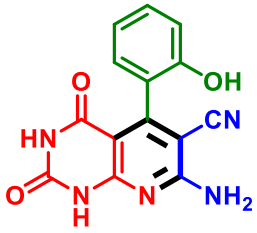
Pale yellow solid (90%), mp >300°C, IR (KBr, cm^{-1}): 3612, 3513, 3282, 2216, 1711, 1585. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.52 (s, 1H), 10.32 (s, 1H), 7.19 (d, 2H), 6.71 (d, 2H), 6.69 (s, 2H), 3.36 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 160.41, 158.46, 157.30, 151.90, 149.28, 137.96, 128.14, 126.99, 123.37, 113.94, 97.71, 86.19, 55.80. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_{11}N_5O_3$ 310.0940; found: 310.0942.

7-amino-5-(3-chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4e)



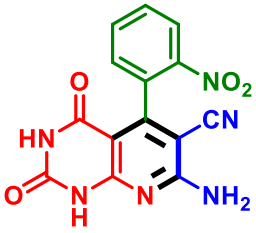
White solid (85%), mp >300°C, IR (KBr, cm^{-1}): 3603, 3520, 3290, 2230, 1720, 1601. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.53 (s, 1H), 10.33 (s, 1H), 7.25 (t, J = 8.1 Hz, 1H), 7.17 (d, J = 9.7 Hz, 1H), 7.09 – 7.01 (m, 2H), 6.70 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 160.08, 159.30, 158.98, 156.28, 151.09, 139.46, 134.14, 129.30, 127.20, 126.99, 125.37, 113.94, 96.61, 82.14. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_8N_5O_2Cl$ 314.0445; found: 314.0443

7-amino-5-(2-hydroxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4f)



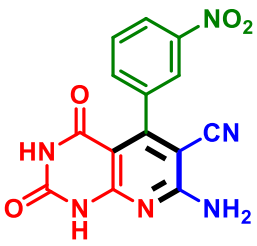
White grey solid (84%), mp >300°C, IR (KBr, cm^{-1}): 3625, 3523, 3291, 2232, 1721, 1598. ^{1}H NMR (500 MHz, DMSO-d^{6}) δ 10.54 (s, 1H), 10.34 (s, 1H), 8.71 (s, 1H), 7.16 (t, 1H), 7.08 – 7.02 (m, 2H), 6.96 (d, 1H), 6.69 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^{6}) δ 160.18, 159.33, 158.18, 156.18, 151.19, 139.47, 134.15, 129.31, 127.21, 126.90, 125.38, 113.95, 96.63, 82.17. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_9N_5O_3$ 296.0784; found: 296.0787

7-amino-5-(2-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4g)



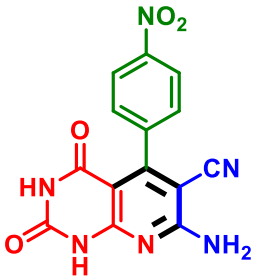
Red solid (89%), mp >300°C, IR (KBr, cm^{-1}): 3624, 3519, 3284, 2227, 1712, 1589. ^{1}H NMR (500 MHz, DMSO-d^{6}) δ 10.55 (s, 1H), 10.35 (s, 1H), 7.76 (d, 1H), 7.61 – 7.51 (m, 2H), 7.35 – 7.31 (m, 1H), 6.68 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^{6}) δ 160.17, 159.40, 158.30, 156.20, 151.20, 139.50, 134.20, 129.33, 127.27, 126.90, 125.40, 113.98, 96.70, 82.20. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_8N_6O_4$ 325.0685; found: 325.0682

7-amino-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4h)



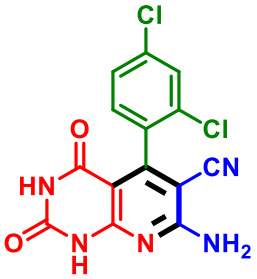
Brown solid (86%), mp >300°C, IR (KBr, cm^{-1}): 3607, 3510, 3279, 2211, 1714, 1579. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.56 (s, 1H), 10.36 (s, 1H), 8.02 (d, 1H), 7.86 (s, 1H), 7.55 – 7.52 (m, 2H), 6.67 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^6) 160.48, 159.45, 155.98, 151.39, 150.28, 148.29, 142.81, 134.28, 129.62, 121.62, 120.76, 115.84, 98.63, 89.18. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_8N_6O_4$ 325.0685; found: 325.0684

7-amino-5-(4-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4i)



Grey solid (93%), mp >300°C, IR (KBr, cm^{-1}): 3604, 3503, 3268, 2209, 1703, 1581. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.41 (s, 1H), 10.21 (s, 1H), 8.10 (d, 2H), 7.40 (d, 2H), 6.66 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 160.49, 159.47, 155.97, 151.38, 150.27, 148.29, 142.82, 128.43, 123.36, 115.81, 98.61, 89.13. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_8N_6O_4$ 325.0685; found: 325.0687

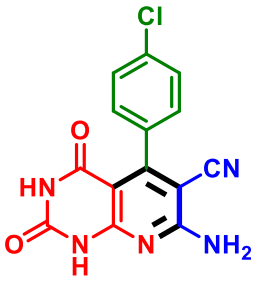
7-amino-5-(2,4-dichlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4j)



Gray solid (91%), mp >300°C, IR (KBr, cm^{-1}): 3605, 3509, 3273, 2212, 1719, 1607. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.31 (s, 1H), 10.21 (s, 1H), 7.51 (s, 1H), 7.41 – 7.32 (m, 2H), 6.65 (s, 2H). ^{13}C NMR

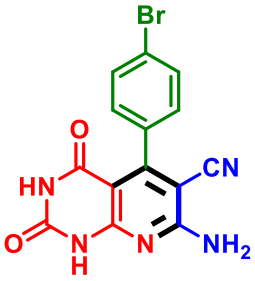
(126 MHz, DMSO-d^6) δ 160.50, 159.43, 155.38, 151.40, 150.24, 148.26, 142.83, 134.27, 129.61, 121.61, 120.56, 115.86, 98.66, 89.21. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_7N_5O_2Cl_2$ 348.0055; found: 348.0055

7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4k)



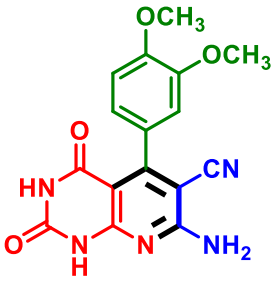
White solid (88%), mp >300°C, IR (KBr, cm^{-1}): 3616, 3519, 3288, 2227, 1715, 1599. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.32 (s, 1H), 10.22 (s, 1H), 7.25 (d, 2H), 7.08 (d, 2H), 6.64 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 160.10, 155.46, 150.30, 148.90, 142.28, 136.96, 127.14, 125.99, 122.37, 111.94, 96.71, 84.19. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_8N_5O_2Cl$ 314.0445; found: 314.0446

7-amino-5-(4-bromophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4l)



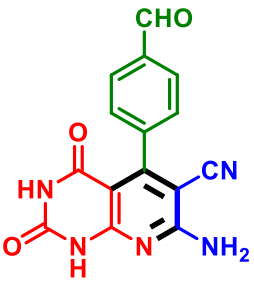
Cream solid (88%), mp >300°C, IR (KBr, cm^{-1}): 3621, 3517, 3291, 2226, 1718, 1589. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.33 (s, 1H), 10.23 (s, 1H), 7.20 (d, 2H), 7.02 (d, 2H), 6.63 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 160.08, 155.06, 150.00, 148.00, 142.08, 136.06, 127.04, 125.59, 122.07, 111.54, 96.31, 84.09. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_8N_5O_2Br$ 357.9940; found: 357.9937

7-amino-5-(3,4-dimethoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4m)



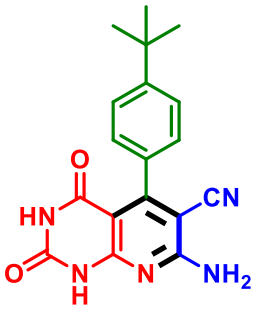
Pale gray solid (91%), mp >300°C, IR (KBr, cm^{-1}): 3624, 3520, 3293, 2224, 1716, 1597. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.34 (s, 1H), 10.24 (s, 1H), 8.40 (d, 1H), 7.93 (d, 1H), 7.14 (s, 1H), 6.62 (s, 2H), 3.87 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 160.50, 159.43, 155.38, 151.40, 150.24, 150.20, 148.83, 137.27, 132.61, 127.61, 122.56, 121.86, 99.56, 89.11, 56.83, 55.80. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{13}N_5O_4$ 340.1045; found: 340.1045

7-amino-5-(4-formylphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile (4n)



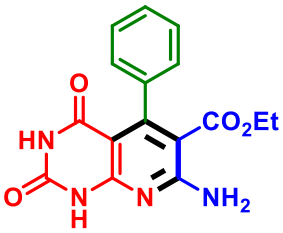
Pale yellow solid (92%), mp >300°C, IR (KBr, cm^{-1}): 3604, 3509, 3271, 2207, 1709, 1603. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.35 (s, 1H), 10.25 (s, 1H), 9.99 (s, 1H), 7.78 (d, 2H), 7.22 (d, 2H), 6.61 (s, 2H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 191.28, 159.08, 156.06, 150.02, 148.20, 142.28, 136.16, 127.14, 125.39, 122.17, 111.44, 96.21, 84.19. HRMS (ESI) m/z: [M+H] + calculated for $C_{15}H_9N_5O_3$ 308.078; found: 308.0783.

Ethyl 7-amino-5-(4-(tert-butyl)phenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4o)



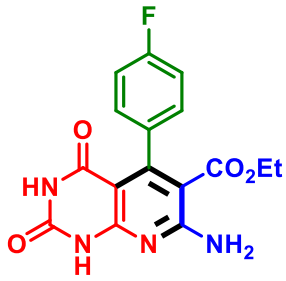
White solid (90%), mp >300°C, IR (KBr, cm^{-1}): 3623, 3531, 3299, 2232, 1727, 1608. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.36 (s, 1H), 10.26 (s, 1H), 7.28 (d, 2H), 7.00 (d, 2H), 6.59 (s, 2H), 1.09 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 160.48, 159.45, 155.98, 153.12, 151.20, 150.28, 139.96, 128.14, 125.37, 115.94, 98.61, 87.07, 31.10, 15.81. HRMS (ESI) m/z: [M+H] + calculated for $C_{20}H_{22}N_4O_4$ 383.1719; found: 383.1716

Ethyl 7-amino-2,4-dioxo-5-phenyl-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carboxylate (4p)



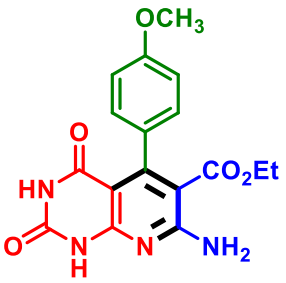
White solid (88%), mp >300°C, IR (KBr, cm^{-1}): 3616, 3512, 3284, 2215, 1711, 1590. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.37 (s, 1H), 10.27 (s, 1H), 7.46 – 7.33 (m, 1H), 7.26 – 7.18 (m, 2H), 7.16 – 7.04 (m, 2H), 6.72 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.89 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.91, 159.38, 159.15, 155.28, 153.22, 151.20, 139.56, 128.24, 124.31, 123.23, 115.90, 98.53, 58.50, 15.71. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{14}N_4O_4$ 327.1093; found: 327.1091

Ethyl 7-amino-5-(4-fluorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4r)



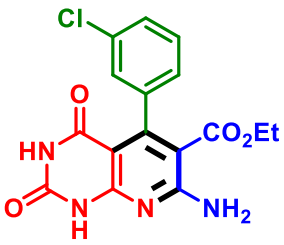
Pinkish gray solid (90%), mp >300°C, IR (KBr, cm^{-1}): 3610, 3505, 3281, 2212, 1718, 1591. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.38 (s, 1H), 10.21 (s, 1H), 7.18 (d, 2H), 6.68 (d, 2H), 6.48 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.90 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.81, 163.11, 159.28, 159.14, 155.14, 153.24, 151.24, 139.52, 128.34, 124.33, 115.89, 98.33, 58.52, 15.01. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{13}N_4O_4F$ 345.0999; found: 345.0997

Ethyl 7-amino-5-(4-methoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4s)



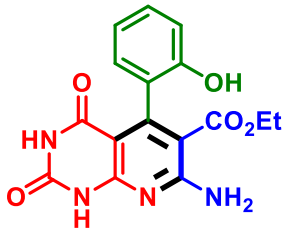
Brown solid (91%), mp >300°C, IR (KBr, cm^{-1}): 3631, 3528, 3299, 2234, 1724, 1601. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.50 (s, 1H), 10.30 (s, 1H), 7.18 (d, 2H), 6.68 (d, 2H), 6.12 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H), 3.37 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.01, 159.08, 159.10, 155.11, 154.11, 153.22, 151.23, 139.32, 128.34, 124.34, 115.79, 98.35, 58.55, 55.01, 15.13. HRMS (ESI) m/z: [M+H] + calculated for $C_{17}H_{16}N_4O_5S$ 357.1199; found: 357.1198

Ethyl 7-amino-5-(3-chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4t)



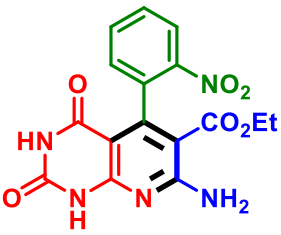
Cream white solid (83%), mp >300°C, IR (KBr, cm^{-1}): 3627, 3525, 3296, 2228, 1719, 1597. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.42 (s, 1H), 10.31 (s, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.13 (d, J = 9.7 Hz, 1H), 7.08-7.00 (m, 2H), 6.13 (s, 2H), 4.15 (q, J = 7.1 Hz, 2H), 3.82 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.81, 159.38, 159.18, 154.12, 153.12, 151.21, 139.31, 134.17, 128.24, 124.37, 121.05, 119.16, 115.79, 98.37, 59.77, 15.15. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{13}N_4O_4Cl$ 361.070; found: 361.073

Ethyl 7-amino-5-(2-hydroxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4u)



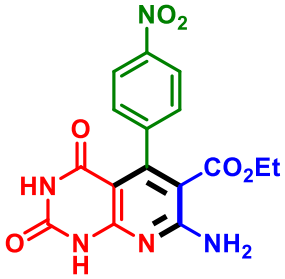
Cream solid (85%), mp >300°C, IR (KBr, cm^{-1}): 3613, 3511, 3280, 2215, 1707, 1591. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.43 (s, 1H), 10.30 (s, 1H), 8.77 (s, 1H), 7.26 (t, 1H), 7.10 – 7.04 (m, 2H), 7.00 (d, 1H), 6.14 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.81, 161.38, 160.18, 155.32, 155.12, 152.21, 150.79, 140.31, 135.17, 129.24, 125.37, 122.05, 114.79, 97.37, 60.77, 14.15. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{14}N_4O_5$ 343.1042; found: 343.1040

Ethyl 7-amino-5-(2-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4v)



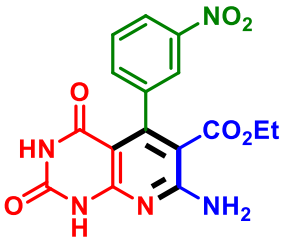
Yellow solid (89%), mp >300°C, IR (KBr, cm^{-1}): 3629, 3527, 3297, 2228, 1724, 1608. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.53 (s, 1H), 10.33 (s, 1H), 7.88 (d, 1H), 7.64-7.54 (m, 2H), 7.36-7.32 (m, 1H), 6.15 (s, 2H), 4.16 (q, J = 7.1 Hz, 2H), 3.78 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.81, 161.39, 160.18, 155.92, 155.82, 152.28, 145.79, 140.61, 135.47, 129.54, 125.57, 122.65, 114.69, 97.67, 60.67, 13.15. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{13}N_5O_6$ 372.0944; found: 372.0945

Ethyl 7-amino-5-(4-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4w)



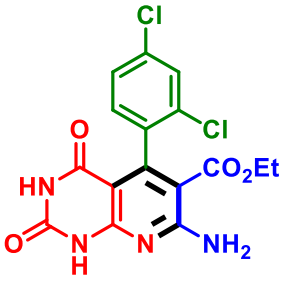
White solid (92%), mp >300°C, IR (KBr, cm^{-1}): 3612, 3504, 3283, 2215, 1711, 1587. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.43 (s, 1H), 10.31 (s, 1H), 7.18 (d, 2H), 6.68 (d, 2H), 6.16 (s, 2H), 4.12 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.81, 160.11, 159.28, 159.14, 155.10, 153.04, 151.54, 139.50, 128.54, 124.53, 115.59, 98.03, 58.50, 16.01. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{13}N_5O_6$ 372.0944; found: 372.0946.

Ethyl 7-amino-5-(3-nitrophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4x)



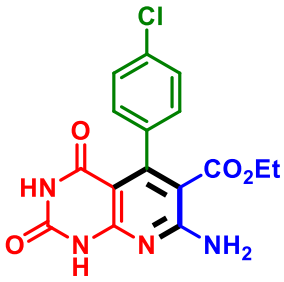
Light yellow solid (85%), mp >300°C, IR (KBr, cm^{-1}): 3616, 3513, 3288, 2217, 1710, 1595. ^{1}H NMR (500 MHz, DMSO-d^{6}) δ 10.37 (s, 1H), 10.17 (s, 1H), 8.02 (d, 1H), 7.86 (s, 1H), 6.70 (s, 2H), 4.21 (q, J = 7.1 Hz, 2H), 3.56 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^{6}) δ 164.81, 161.39, 160.18, 155.92, 155.82, 152.28, 145.79, 140.61, 135.47, 129.54, 125.57, 122.65, 114.69, 97.58, 58.67, 17.15. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{12}N_4O_4Cl_2$ 395.0313; found: 395.0315

7-amino-5-(2,4-dichlorophenyl)-6-((ethylperoxy)-l2-methyl)pyrido[2,3-d]pyrimidine-2,4(1H,3H)-dione (4y)



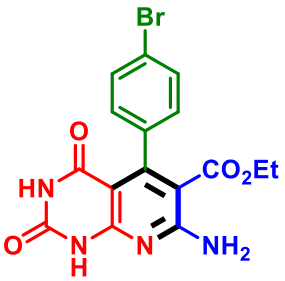
Light yellow solid (89%), mp >300°C, IR (KBr, cm^{-1}): 3616, 3513, 3288, 2217, 1710, 1595. ^{1}H NMR (500 MHz, DMSO-d^{6}) δ 10.54 (s, 1H), 10.34 (s, 1H), 7.50 (s, 1H), 7.41 – 7.37 (m, 2H), 6.77 (s, 2H), 4.20 (q, J = 7.1 Hz, 2H), 3.59 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^{6}) δ 164.72, 161.00, 160.10, 155.72, 155.72, 152.18, 145.71, 140.61, 135.47, 129.54, 125.59 , 122.69, 114.69, 97.70, 58.60, 18.01. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{12}N_4O_4Cl_2$ 395.0313; found: 395.0315

Ethyl 7-amino-5-(4-chlorophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4z)



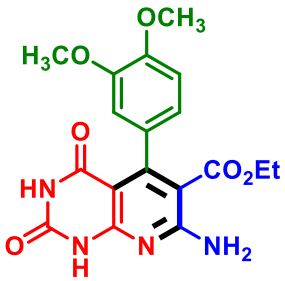
Yellow solid (88%), mp >300°C, IR (KBr, cm^{-1}): 3611, 3507, 3280, 2212, 1711, 1590. ^{1}H NMR (500 MHz, DMSO-d^{6}) δ 10.53 (s, 1H), 10.33 (s, 1H), 7.25 (d, 2H), 7.08 (d, 2H), 6.17 (s, 2H), 4.10 (q, J = 7.1 Hz, 2H), 3.20 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^{6}) δ 164.81, 160.61, 159.60, 155.56, 153.04, 151.52, 139.40, 130.13, 128.29, 124.25, 115.16, 98.03, 58.59, 16.11. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{13}N_4O_4Cl$ 61.0703; found: 61.0700

Ethyl 7-amino-5-(4-bromophenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d] pyrimidine-6-carboxylate (4za)



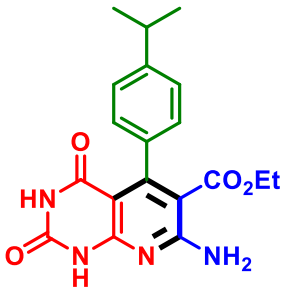
White solid (87%), mp >300°C, IR (KBr, cm^{-1}): 3619, 3518, 3291, 2224, 1718, 1598. ^{1}H NMR (500 MHz, DMSO-d^{6}) δ 10.54 (s, 1H), 10.36 (s, 1H), 7.15 (d, 2H), 6.98 (d, 2H), 6.18 (s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 3.10 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^{6}) δ 164.81, 160.49, 159.47, 155.36, 153.18, 151.13, 139.01, 130.00, 128.01, 124.05, 115.04, 98.01, 58.48, 16.16. HRMS (ESI) m/z: [M+H] + calculated for $C_{16}H_{13}N_4O_4Br$ 405.0198; found: 405.0199

Ethyl 7-amino-5-(3,4-dimethoxyphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4zb)



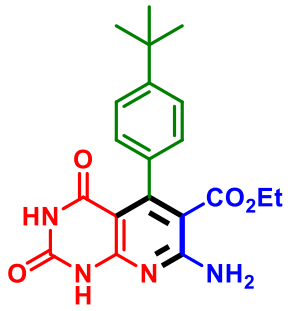
White solid (91%), mp >300°C, IR (KBr, cm^{-1}): 3613, 3510, 3281, 2214, 1711, 1585. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.55 (s, 1H), 10.35 (s, 1H), 8.28 (s, 1H), 7.93 (d, 1H), 7.14 (d, 1H), 6.24 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 3.77 (s, 3H),3.13 (s, 3H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.18, 161.16, 160.02, 155.62, 155.72, 152.81, 145.61, 140.69, 135.17, 129.52, 125.49 , 122.70, 114.69, 97.70, 58.60, 18.01, 56.83, 55.80. HRMS (ESI) m/z: [M+H] + calculated for $C_{18}H_{18}N_4O_6$ 387.1304; found: 387.1302

Ethyl 7-amino-5-(4-isopropylphenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4zc)



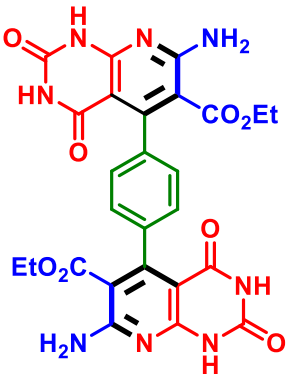
Cream white (88%), mp >300°C, IR (KBr, cm^{-1}): 3617, 3513, 3282, 2225, 1711, 1590. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.56 (s, 1H), 10.36 (s, 1H), 7.88 (d, 2H), 7.55 (d, 2H), 6.71 (s, 2H), 4.22 (q, J = 7.1 Hz, 2H), 3.15 (s, 3H), 2.90-2.85 (m, 1H), 1.23 (d, J = 6.9 Hz, 6H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.90, 161.48, 158.45, 153.98, 151.30, 139.96, 128.14, 126.99, 125.37, 115.94, 98.75, 88.18, 60.60, 38.2, 28.2, 18.01. HRMS (ESI) m/z: [M+H] + calculated for $C_{19}H_{20}N_4O_4$ 369.1562; found: 369.1560

Ethyl 7-amino-5-(4-(tert-butyl)phenyl)-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate (4zd)



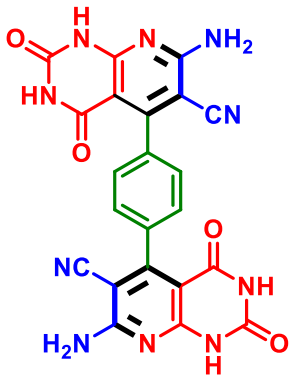
White solid (87%), mp >300°C, IR (KBr, cm^{-1}): 3610, 3507, 3279, 2209, 1703, 1582. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.48 (s, 1H), 10.31 (s, 1H), 7.20 (d, 2H), 7.02 (d, 2H), 6.30 (s, 2H), 4.32 (q, J = 7.1 Hz, 2H), 3.80 (s, 3H), 1.10 (s, 9H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 165.91, 160.48, 159.45, 155.98, 153.12, 151.20, 150.28, 139.96, 128.14, 125.37, 115.94, 98.61, 58.51, 34.18, 31.10, 15.81. HRMS (ESI) m/z: [M+H] + calculated for $C_{20}H_{22}N_4O_4$ 383.1719; found: 383.1717.

Diethyl 5,5'-(1,4-phenylene)bis(7-amino-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carboxylate) (4ze)



White solid (86%), mp >300°C, IR (KBr, cm^{-1}): 3621, 3520, 3290, 2227, 1718, 1602. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.41 (s, 2H), 10.21 (s, 2H), 7.10 (d, 4H), 6.69 (s, 4H), 4.07 (q, J = 7.1 Hz, 4H), 3.08 (s, 6H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 164.93, 159.31, 159.13, 155.21, 153.23, 151.21, 139.53, 128.21, 115.91, 98.53, 58.51, 15.73. HRMS (ESI) m/z: [M+H] + calculated for $C_{14}H_{13}N_2O_2S_2$ 575.1638; found: 575.1640

5,5'-(1,4-phenylene)bis(7-amino-2,4-dioxo-1,2,3,4-tetrahydropyrido[2,3-d]pyrimidine-6-carbonitrile) (4zf)



White solid (88%), mp >300°C, IR (KBr, cm^{-1}): 3619, 3517, 3289, 2223, 1717, 1597. ^{1}H NMR (500 MHz, DMSO-d^6) δ 10.42 (s, 2H), 10.22 (s, 2H), 7.16 (d, 4H), 6.37 (s, 4H). ^{13}C NMR (126 MHz, DMSO-d^6) δ 160.48, 159.45, 155.98, 150.28, 139.96, 128.14, 115.94, 98.61, 89.14. HRMS (ESI) m/z: [M+H] + calculated for $C_{22}H_{12}N_{10}O_4$ 481.1121; found: 481.1124.

5.8 Spectral Data of few product

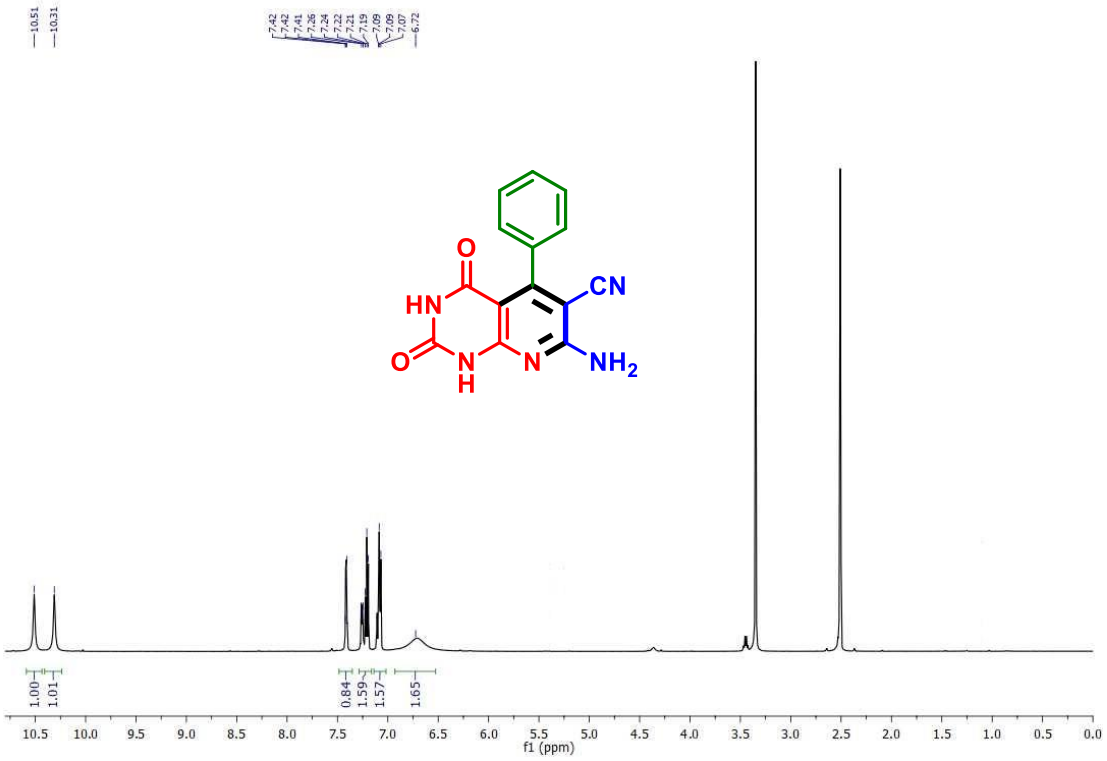


Figure 5.2 ^{1}HNMR of product **4a**

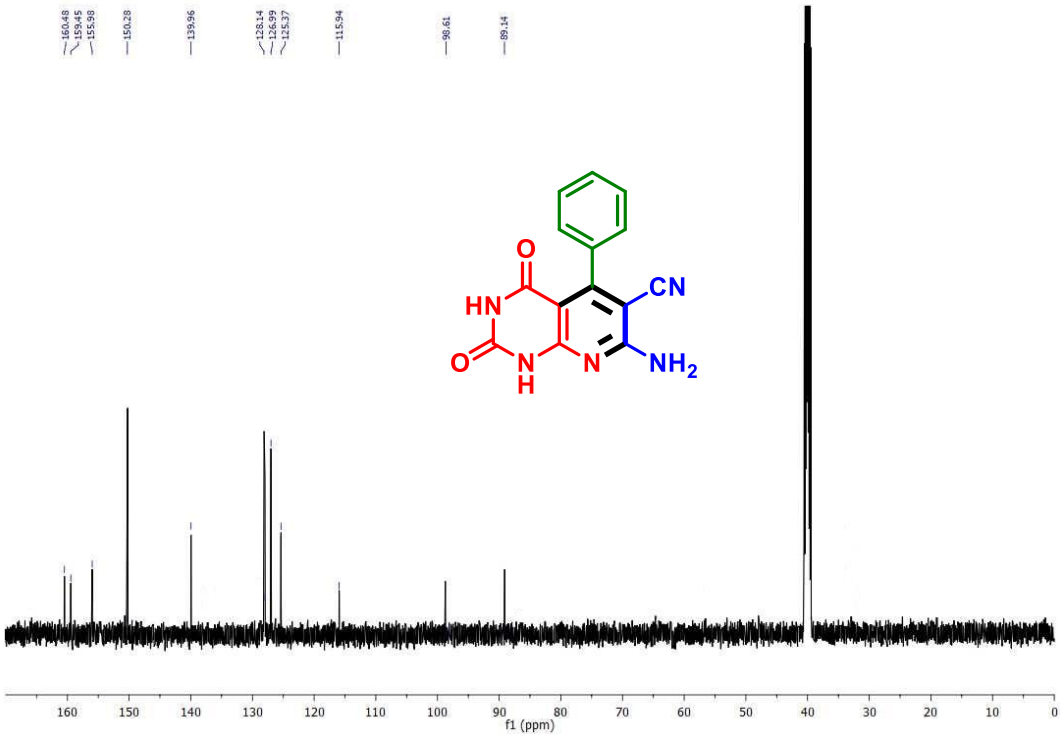


Figure 5.3 ^{13}CNMR of product **4a**

5.9 HRMS spectra

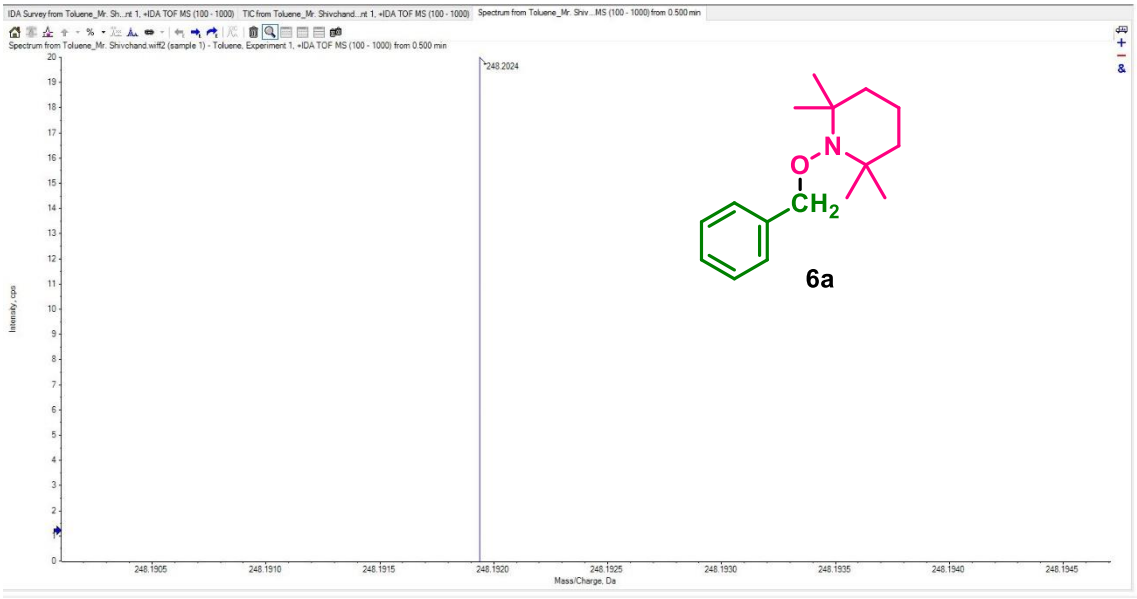


Figure 5.4 HRMS Spectra of **6a**

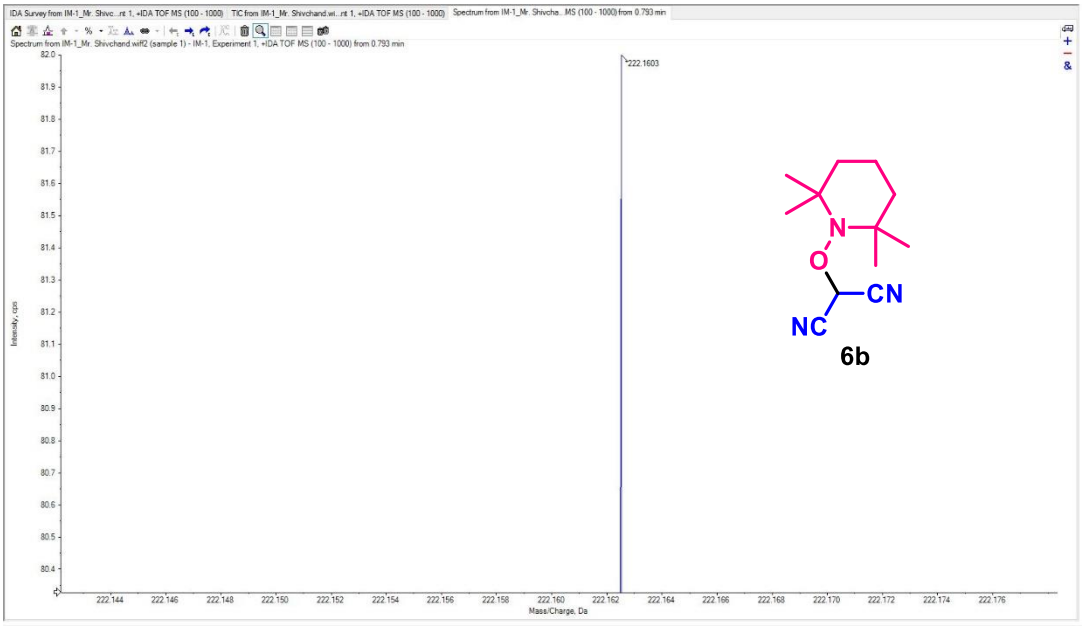


Figure 5.5 HRMS Spectra of **6b**

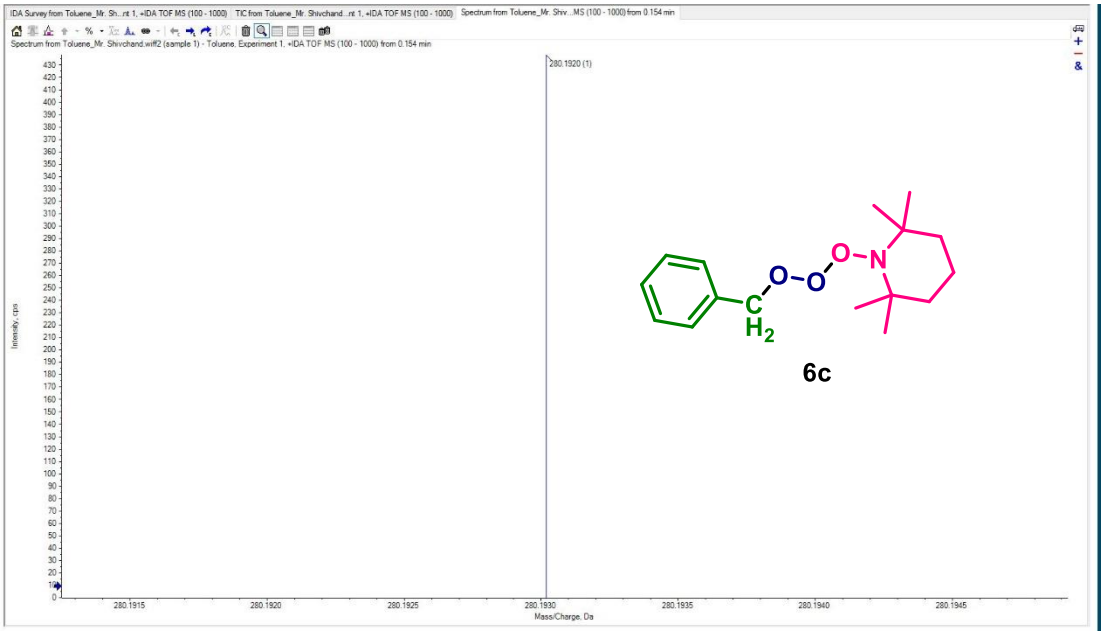


Figure 5.6 HRMS Spectra of **6c**

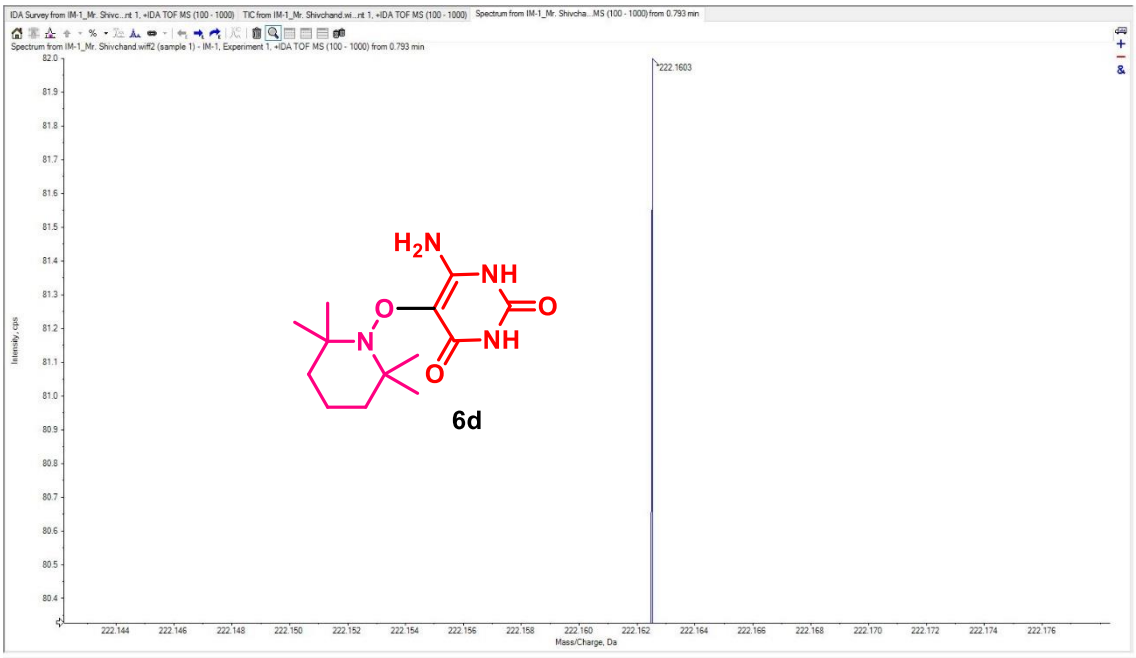


Figure 5.7 HRMS Spectra of **6d**

5.10 References

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