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RESEARCH ARTICLE

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Cobalt perchlorate hexahydrate catalyzed one-pot synthesis of dihydropyrimidin-ones/-thiones through sonochemistry and its mechanistic study using density functional theory calculations

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Abstract

A cobalt(II) perchlorate hexahydrate coordinated synthesis of dihydropyrimidin-ones and -thiones through sonochemistry is developed. Herein, the reaction was demonstrated as a simple, efficient, and one-pot method for synthesizing a series of interesting 3,4-dihydropyrimidin-2(1H)-ones. Further, the reaction mechanism was investigated using mass spectrometry and density functional theory calculations suggesting that a Lewis acid character of cobalt(II) perchlorate hexahydrate plays a crucial role in coordinating carbonyl functionalities and stabilizing the polar intermediates like imine–enamine which further led to cyclized dihydropyrimidin-ones and -thiones. This methodology was further explored to synthesize a gram-scale synthesis of monastrol drug, a kinase inhibitor.

1 | INTRODUCTION

Reactions involving three or more reactants in a single vessel resulting in a product containing all reactant's atoms are called multi-component reactions (MCRs) [1–4]. These facilitate the generation of small and diverse organic molecules compared to linear synthesis. MCRs hugely impact organic synthesis because of the atom and energy economy [5]. This gives medicinal chemists a powerful tool to create diverse spaces of biological targets [6], different MCRs involve chemicals like isocyanides (Passerini [7] and Ugi coupling [8]) and acetoacetate (Biginelli [9] and Hantzsch). Biginelli reaction is one of the most used MCRs, first reported in 1893 by Pietro Biginelli. It allows the synthesis of biologically active molecules like 3,4-dihydropyrimidin-2(1H)-one (DHPM) derivatives in a single-step reaction [10–12]. DHPMs have a structural resemblance to that of clinically active Hantzsch pyridines [13]. Pyrimidines display a wide range of biological activities, including enastron [14], piperastrol [15], monastrol [16], and (*R*)-SQ 32926 (Figure 1) [17].

In the past, pyrimidinones have been reported as calcium channel modulators [13, 18], adrenergic receptor antagonists, mitotic kinesin inhibitors [14], antiviral, and antibacterial [19]. Biginelli reaction has several limitations like long reaction times, low yields [20], low ee's [19], and requirement of synthesis of catalysts. Many attempts were made to overcome these limitations and improve the yields, shortening reaction time [20] and increasing selectivity for the desired product [21]. Many Lewis acid catalysts like $SbCl_3$ [22], $Cu(OTf)_2$ [23], $ZrCl_4$, $FeCl_3$ [24], $SnCl_2$, $InBr_3$ [25, 26], $ZnBr_2$ [27], and $Mg(ClO_4)_2$ [28, 29] were proved the capability in promoting the Biginelli reaction. However, many issues associated with their use are the high cost, long reaction time, and moderated yield. Therefore, efforts were made by the different research groups to develop a method for

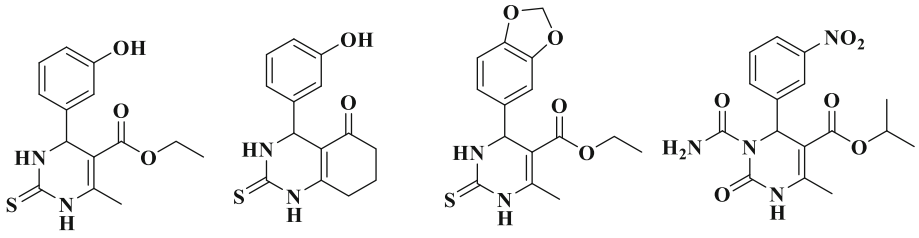


FIGURE 1 Dihydropyrimidine scaffold as important drugs.

shortening the reaction time with a better yield of desired DHPM products. Some important previous research works include using indium(III) chloride [30], imidazolium-based ionic liquids [31], and chiral Bronsted ionic liquid found successful through the Biginelli reaction [32]. Sonochemistry or ultrasound-assisted organic synthesis is a useful, sustainable, or eco-friendly methodology for efficient, economical, and faster synthesizing complex molecules. Therefore, the use of sonochemistry is increasing nowadays than the traditional synthetic methods [33].

Continuing our endeavors to develop simple methods for synthesizing dihydropyrimidine derivatives, we herein reported a one-pot MCR through sonochemistry catalyzed by cobalt(II) perchlorate hexahydrate. Cobalt(II) perchlorate hexahydrate was a better catalyst than previous reports to afford DHPMs with a high yield in a shorter reaction time.

2 | RESULTS AND DISCUSSION

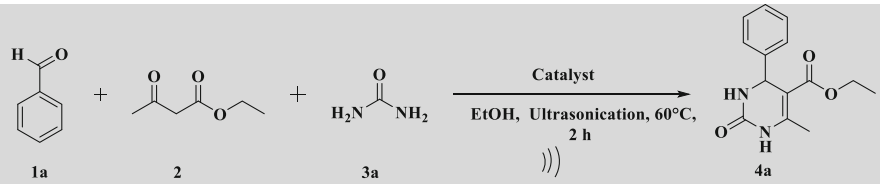
To develop an economical, sustainable, and easy synthesis of DHPMs, we initially performed a model reaction using three components, that is, benzaldehyde (**1a**), ethyl acetoacetate (EAA; **2**), and urea (**3a**). The effect of the catalyst was investigated as the Biginelli reaction promoter (Table 1). It is worth highlighting that all reactions were conducted with equimolar quantities of the three components of the Biginelli reaction under ultrasonication/ultrasound. The reaction was monitored within 0.5, 1, 1.5, and 2 h with a continuous observation till 2 h at 60°C would lead to the optimum yield of the desired DHPM (**4a**) under ultrasonication. Entry 1 in Table 1 represents the reaction without using the catalyst to yield DHPM (**4a**) in 45%. A series of acids like concd HCl, concd H_2SO_4, and glacial AcOH were found to give a good yield of the DHPM in 58%–62% (Entries 2–4, Table 1). Using different Lewis acids catalysts like $FeCl_3$, $ZnCl_2$, $MgCl_2$, $FeCl_3{\cdot}6H_2O$, $BF_3{\cdot}OEt_2$, $SnCl_2$, $CuCl_2$, NH_4Cl, and $NaOI_4$ showed similar results without much improvement in the yield of 56%–64% (Entries 5–13, Table 1). Perchlorates are the promising catalyst reported for their catalytic potential in various reactions [34–36] and DHPM synthesis but are found to be less efficient [37, 38].

Herein different perchlorate catalysts were used, which showed good improvements for Biginelli reaction as promoters to yield the DHPM (**4a**) like $Mg(ClO_4)_2{\cdot}6H_2O$, $LiClO_4{\cdot}3H_2O$, $Co(ClO_4)_2{\cdot}6H_2O$, $NaClO_4$, $KClO_4$, $Al_3ClO_4{\cdot}9H_2O$, $Ni(ClO_4)_2{\cdot}6H_2O$, in 88%, 89%, 92%, 82%, 78%, 80%, and 77%, respectively (Entries 14–20 Table 1). $Co(ClO_4)_2{\cdot}6H_2O$ was the best catalyst; this may be due to good solubility in organic solvent and better coordination power Co^{+2} to carbonyl functionality [39]. Further, its mol % was increased from 20% to 30%, and 40% (compare Entries 16, with 21 and 22, Table 1) but resulted in a lesser yield, which may be due to saturation of the catalyst leading to equilibrium shifting toward the reactant. Further, we tried the conventional reaction with $Co(ClO_4)_2{\cdot}6H_2O$ as catalyst mol% of 20% and 30% (Entries 23 and 24, Table 1). Still, there is no yield improvement and its longer reaction time compared to the ultrasonication condition, suggesting the comprehensive role of sonochemistry in improving the course of DHPM synthesis catalyzed by $Co(ClO_4)_2{\cdot}6H_2O$. We also tried a reaction with a decreased amount of the cobalt catalyst to 10 mol% but led to a lower yield of 64% (Entry 25, Table 1).

Due to better yield, the $Co(ClO_4)_2{\cdot}6H_2O$ is chosen for further screening of solvents (Table 2). Entry 1 showed that without a solvent reaction, affording 50% of yield. Further, a series of protic polar solvents were utilized (Entries 2–6, Table 2); among them, ethanol was found to be most promising, with a 92% yield (Entry 4, Table 2), while water led to a 30% yield due to poor solubility of starting materials (Entry 2, Table 2). Ethanol serves as a suitable solvent and is also one of the environmentally benign, safer, and greener solvents for chemical synthesis [39]. The non-polar solvents yielded moderate due to poor solubility (Entries 7–9, Table 2). Aprotic polar solvents showed moderate yields (Entries 10–19, Table 2). It is noted that adding ethanol in a water-mediated reaction in equal portions (v/v) led to an increase in yield from 30% to 54% (Entry 20, Table 2).

We explore the electrospray ionization (ESI)–high-resolution mass spectrometry (HRMS) technique to

TABLE 1 Screening of the catalyst for the synthesis of 3,4-dihydropyrimidin-2(1H)-one (DHPM).[a]



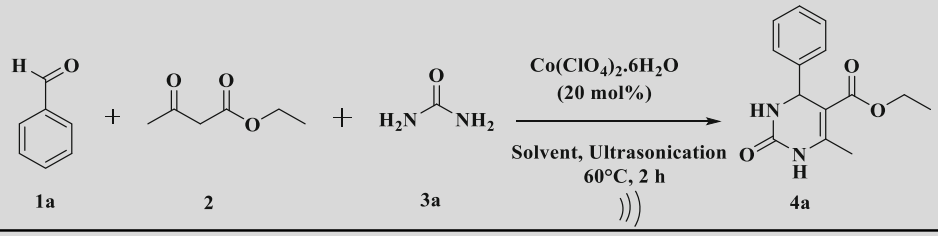
1a 2 3a 4a

Entry	Catalyst	4a, yield (%)[b]
1	–	45
2	Concd HCl	58
3	Concd H_2SO_4	62
4	Glacial AcOH	62
5	$ZnCl_2$	56
6	$MgCl_2{\cdot}6H_2O$	64
7	$AlCl_3{\cdot}3H_2O$	63
8	$FeCl_3{\cdot}6H_2O$	58
9	$BF_3{\cdot}OEt_2$	59
10	$SnCl_2$	60
11	$CuCl_2$	62
12	NH_4Cl	55
13	$NaOI_4$	63
14	$Mg(ClO_4)_2{\cdot}6H_2O$	88
15	$LiClO_4{\cdot}3H_2O$	89
16	$Co(ClO_4){\cdot}6H_2O$	92
17	$NaClO_4$	82
18	$KClO_4$	78
19	$Al_3ClO_4{\cdot}9H_2O$	80
20	$Ni(ClO_4)_2{\cdot}6H_2O$	77
21	$Co(ClO_4)$ $6H_2O$ (30 mol%)	88
22	$Co(ClO_4)$ $6H_2O$ (40 mol%)	89
23	$Co(ClO_4)$ $6H_2O$ (20 mol%) conventional reaction[c]	78
24	$Co(ClO_4){\cdot}6H_2O$ (30 mol%) conventional reaction[c]	83
25	$Co(ClO_4){\cdot}6H_2O$ (10 mol%)	64

[a]All reactions were performed with 2 mmol of **1a** (1 equiv), **2** (1 equiv), and **3a** (1 equiv) in 5 mL of ethanol as a solvent in the presence of 20 mol% catalysts other than specified at 60°C in ultrasonication till 2 h.
[b]Isolated yields DHPM (**4a**).
[c]These reactions were performed without ultrasonication under conventional heating at 60°C.

examine the effect of a catalyst and its reaction mechanism. Three different types of Biginelli reaction mechanisms were accepted: the iminium mechanism, Knoevenagel mechanism, and enamine mechanism [32, 40, 41]. But till today, these mechanisms are not fully established. An ESI–mass spectrometry (ESI–MS and -MS/MS) was recently used to better understand the Biginelli reaction mechanism by identifying the intermediates generated during the transition from reactant to product [42]. Since ESI–MS can be used to identify and suggest the masses of intermediates, it is helpful in understanding the involvement of different intermediates in the reaction mechanism [43]. A catalytic cycle was proposed based on the observations and interpretations of ESI–HRMS spectra (Figure S105). An ESI–HRMS spectrum of the reaction mixture was analyzed, which displayed the peak at m/z 131.0708 (calcd 131.0700 for M + H) for the starting material, that is, EAA (Figure S105 [i]), while the addition of $Co(ClO_4)_2{\cdot}6H_2O$ in a reaction mixture led to m/z 190.0035 (calcd 190.0105 for M + H)

TABLE 2 Screening of different solvents to optimize the synthesis of 3,4-dihydropyrimidin-2(1H)-one (DHPM).[a]



Entry	Solvent	4a, yield (%)[b]
1	Neat	50
2	H_2O	30
3	Methanol	71
4	Ethanol	92
5	Isopropyl alcohol	80
6	*n*-Butanol	70
7	*n*-Hexane	60
8	Toluene	65
9	Benzene	50
10	Acetonitrile	65
11	Dichloromethane	58
12	Dichloroethane	58
13	Chloroform	60
14	Ethyl acetate	62
15	Tetrahydrofuran	50
16	Dimethyl sulfoxide	43
17	*N,N*-Dimethylformamide	67
18	1,4-Dioxane	63
19	Acetone	66
20	H_2O and ethanol (1:1)	54

[a]All reactions were performed with 2 mmol of **1a** (1 equiv), **2** (1 equiv), and **3a** (1 equiv) in 5 mL of solvent in the presence of 20 mol% of $Co(ClO_4)_2{\cdot}6H_2O$ at 60°C in ultrasonication till 2.
[b]Isolated yields DHPM (**4a**).

for a possible cobalt coordinated structure with both carbonyls of EAA (structure-**a**, Figure S105[ii], and Figure 2).

The cobalt coordinated structure was also observed via UV absorbance study. EAA (**2**) showed two wavelength maxima peaks at 240 and 275 nm (at 200 μM concentration). When cobalt metal was added to the reaction, it formed a complex with EAA, leading to a single wavelength maxim at 275 nm, while a peak at 240 μM disappeared (Figure 3). This suggests the formation of a good coordination complex with cobalt and carbonyl functionalities that led to increasing the electrophilicity of carbonyl carbon which helps in the nucleophilic attack of urea (A poor nucleophile) as observed in a peak at *m/z* 250.0353 (calcd 250.0681 for M + H) (structure-**b**, Figure S105[iii], and Figure 2).

Further, it leads to imine intermediate (structure-**c**, Figure S105[iv], and Figure 2) via dehydration, and it remains in equilibrium with enamine (structure-**d**, Figure S105[iv], and Figure 2) speculated by the peaks at *m/z* 232.0253 (calcd 232.0681 for M + H) and 197.0892 (calcd 197.0771 for M+), respectively. Further enamine attack to the carbonyl of aldehyde and forming an aldol type of intermediate complexes with cobalt as observed at *m/z* 338.0671 (calcd 338.1003 for M + H) (see structure-**e**, Figure S105[v], and Figure 2). After that, an intramolecular condensation of the Biginelli product **4a** (Figure S105[vi], and Figure 2) was formed which is observed at *m/z* 261.1239 (calcd 261.1230 for M + H). Based on the ESI–HRMS we proposed the mechanism of the Biginelli reaction via cobalt-catalyzed electrophilic activation forming an imine (structure **c**) and enamine (structure **d**) intermediate from EAA and

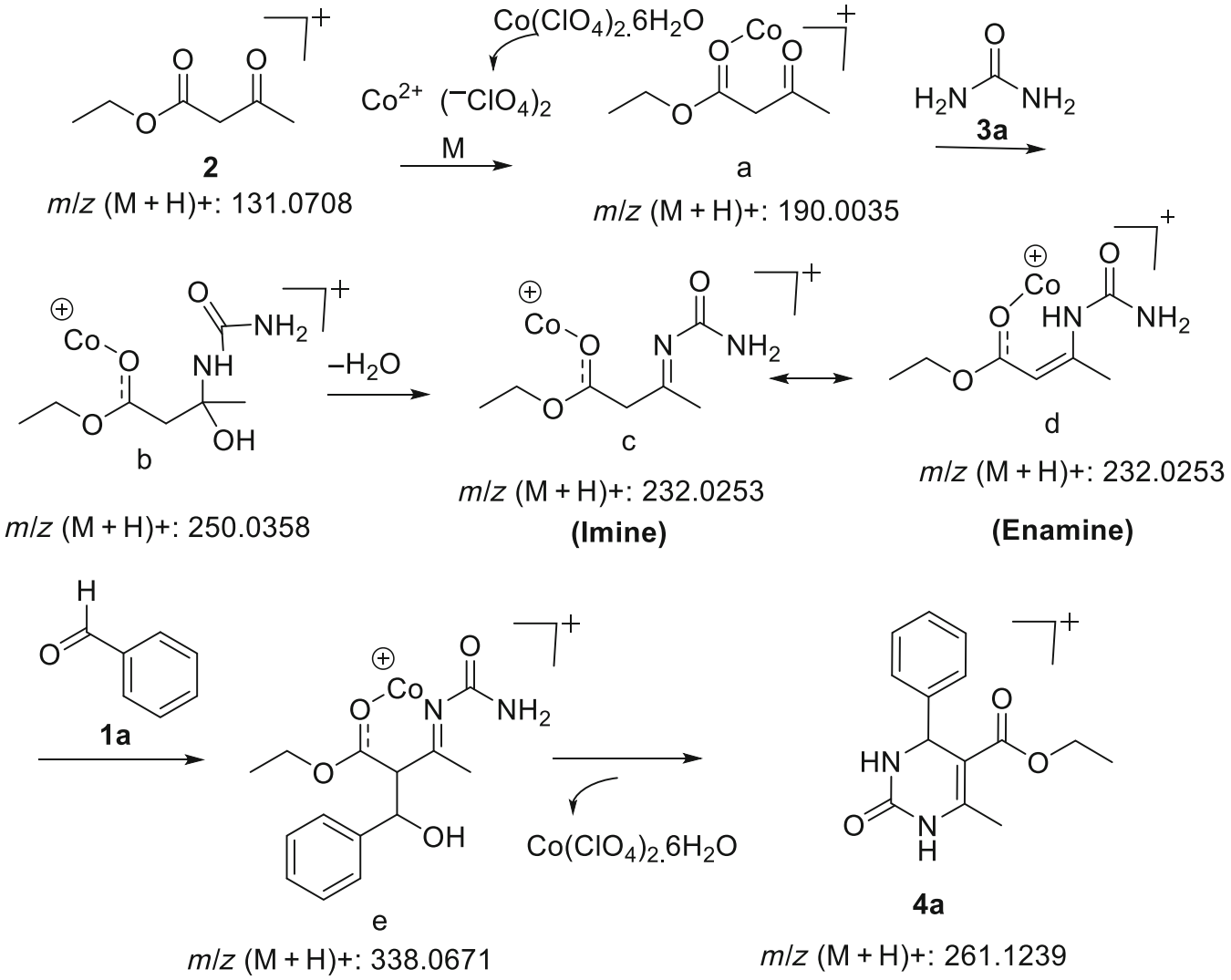


FIGURE 2 Plausible reaction mechanism via imine and enamine intermediates and identification of reactive intermediate via electrospray ionization–high-resolution mass spectrometry and studied by density functional theory calculations.

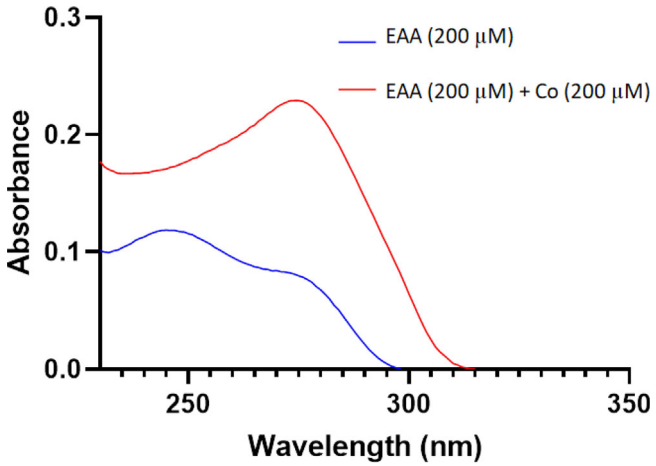
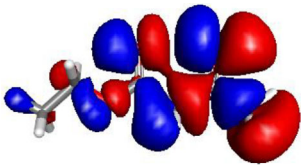
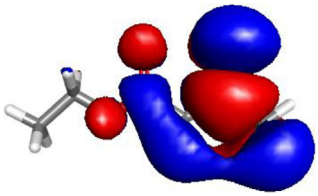
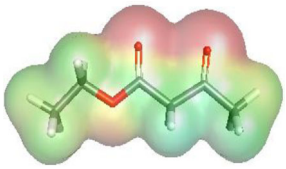
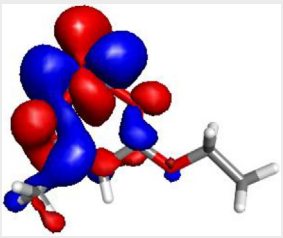
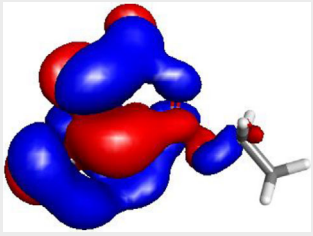
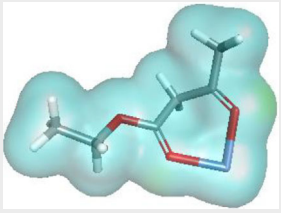
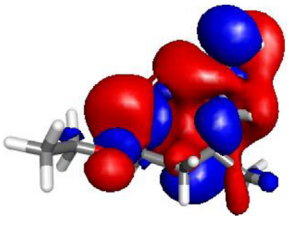
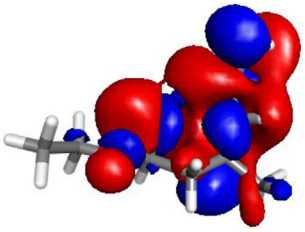
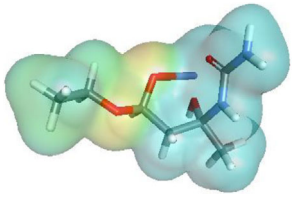
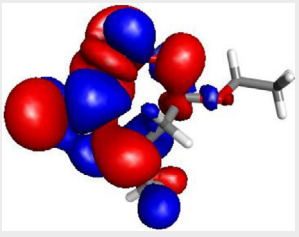
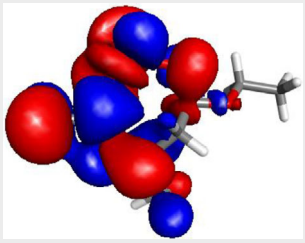
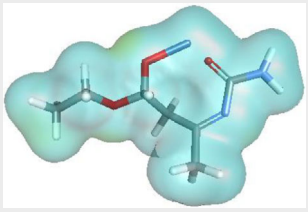
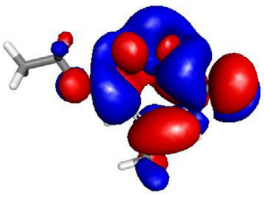
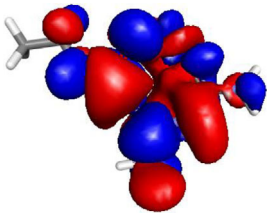
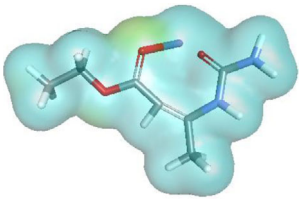
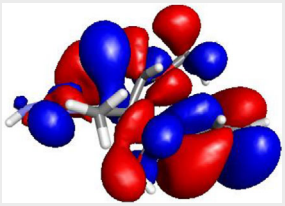
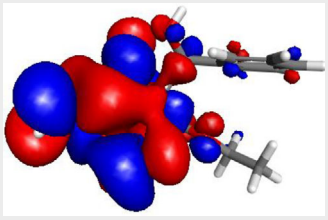
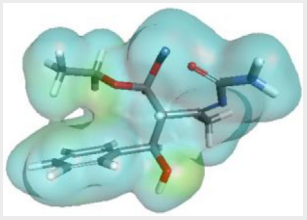
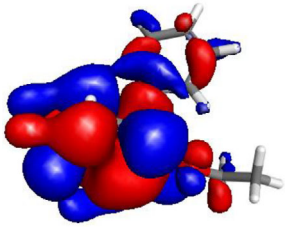
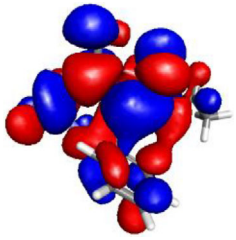
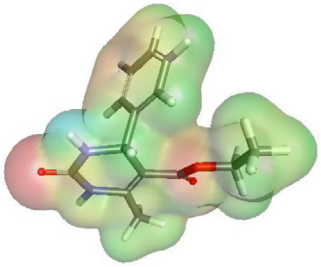


FIGURE 3 UV study of ethyl acetoacetate (EAA) and cobalt complex at 200 μM concentration in ethanol.

urea (Figure 2). Further enamine attack on the electrophilic carbonyl carbon of aldehyde to give aldol type intermediate which undergoes intramolecular condensation via the attack of an amino group into the cyclic DHPM via dehydration.

Further, to establish the proposed reaction mechanism, we performed quantum mechanics calculation using Discovery Studio 2021. We calculated various molecular and atomic properties using density functional theory (DFT) implemented in DMol3 (it can efficiently optimize the structure of molecular systems) [44]. According to DFT analysis, the molecules' lower kinetic stability and higher chemical reactivity in terms of molecular interactions or charge transfer interactions with other molecules are indicated by a smaller gap between the highest occupied molecular orbital (HOMO) and

TABLE 3 HOMO, LUMO, and MEP identification by density functional theory calculations of structures of molecules (from Figure 2).

Molecule number	Molecule code	HOMO	LUMO	MEP
1.	**2**			
2.	**a**			
3.	**b**			
4.	**c**			
5.	**d**			
6.	**e**			
7.	**4a**			

Abbreviations: HOMO, highest occupied molecular orbital; LUMO, lowest unoccupied molecular orbital; MEP, molecular electrostatic potential (positive, negative, and intermediate electrostatic potential sites were represented on the surface by the blue, red, and green color, respectively).

lowest unoccupied molecular orbital (LUMO) [45, 46]. DFT analysis was used to determine the HOMO and LUMO frontier orbital for the intermediates and molecular electrostatic potential (atomic units [a.u.]) (**2–4a**), as shown in Table 3. The red and blue regions show the electrophilic and nucleophilic regions in the molecule, respectively [47]. These optimized structural models showed by the HOMO an electropositive area localized on C═O, C═O, and (O) groups (Figure 4), and C═O are the preferred sites for nucleophilic attack when the metal ion forms the complex.

The energies derived from the DFT study were then used to determine additional parameters related to compound stability. The smaller HOMO–LUMO gap, also known as the energy gap, denotes a compound with lower stability and increased reactivity, as shown in Figure 4 [48].

Further, using Becke's three-parameter exchange functionals (B3LYP) method of the Dmol3 package of BIOVIA DS 2021, the frontier orbital energies or HOMO and LUMO were computed for different possible structures of molecules (**1–7**, Table 4, Table S1) [49]. The HOMO and LUMO energy levels characterize molecules' electron donor and acceptor character. We calculated the HOMO–LUMO gap between intermediate **2** and **a** (complex) by examining the HOMO and LUMO energy profiles [48, 50]. As a metal complex form, a decrease in calculated HOMO energy while an increase in total energy and LUMO energies is observed (molecules **1** and **2**, Table 4, Table S1). The same is represented in Figure 4, a HOMO–LUMO gap for molecule **2** found to be 6.35 eV, which decreased to 2.9 eV after forming the cobalt complex (**a**).

A comparison of the total energy, HOMO energy, LUMO energy, and HOMO–LUMO gap is plotted in Figure 5. Figure 5A progresses as proposed in Figure 2, which shows the decrease in total energies after forming the metal complex and the final product liberated from the cobalt complex again, increasing the total energy. The same correlated via HOMO, LUMO energies changes given in Figure 5B,C showing the initial decrease in HOMO–LUMO gap and later increase to

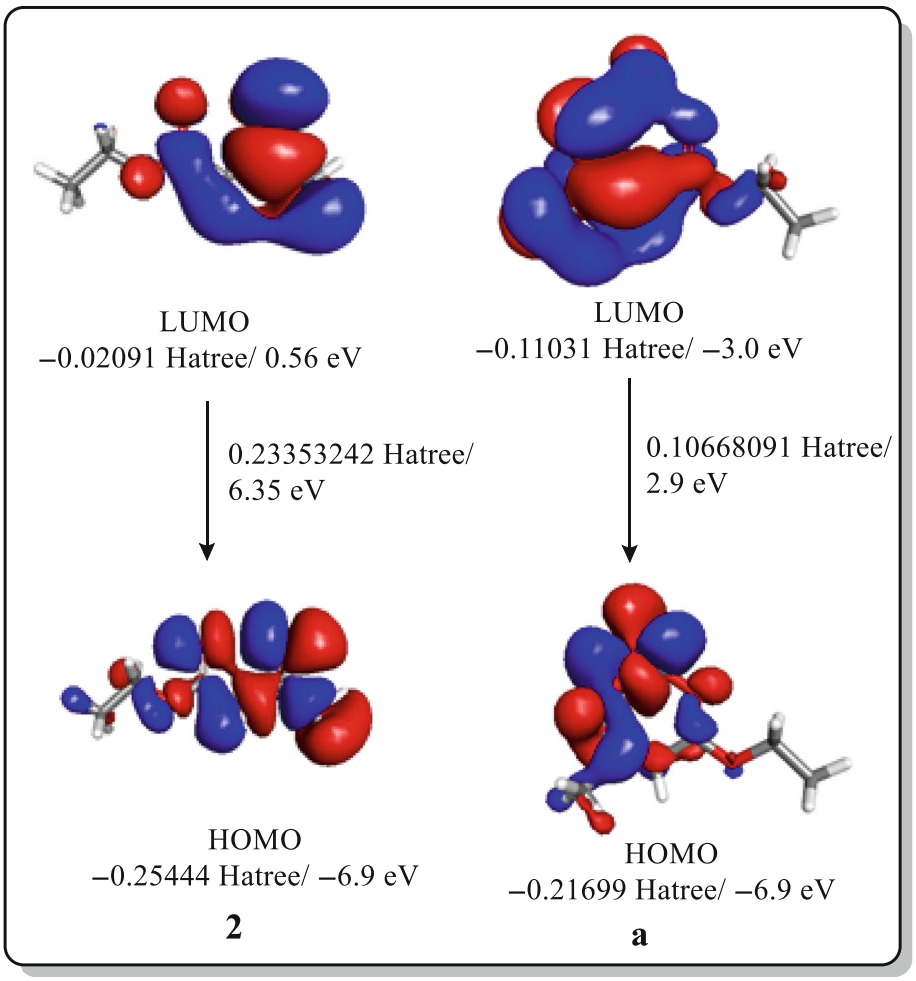


FIGURE 4 (A) Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy gap of molecule **2** and (B) HOMO and LUMO energy gap of molecule **a** (Cobalt complex with **2**).

TABLE 4 Molecular orbital energy calculations of structures of molecules from density functional theory.

Molecule number	Molecule code	Total energy (eV)	HOMO energy (eV)	LUMO energy (eV)	HOMO-LUMO gap (eV)
1	2	−13,251.720116	−6.9236676318	−0.5689902931	6.3547431902
2	a	−51,760.613542	−5.9046008466	−3.0016891073	2.9029365017
3	b	−58,208.773917	−3.9241554362	−3.9241554362	0.0000087076
4	c	−56,034.212013	−5.86704912	−5.86704912	0.0000206807
5	d	−56,017.66947	−5.2735685703	−3.1140721733	2.159434355
6	e	−66,012.639464	−6.9448925208	−3.8645624786	3.0801752093
7	4a	−25,313.581285	−6.3582148202	−1.2253291678	5.1330657918

Abbreviations: HOMO energy, the energy of the highest occupied molecular orbital; HOMO–LUMO gap, the energy difference between LUMO and HOMO; LUMO energy, the energy of the lowest unoccupied molecular orbital; Total energy, the total energy of the molecule.

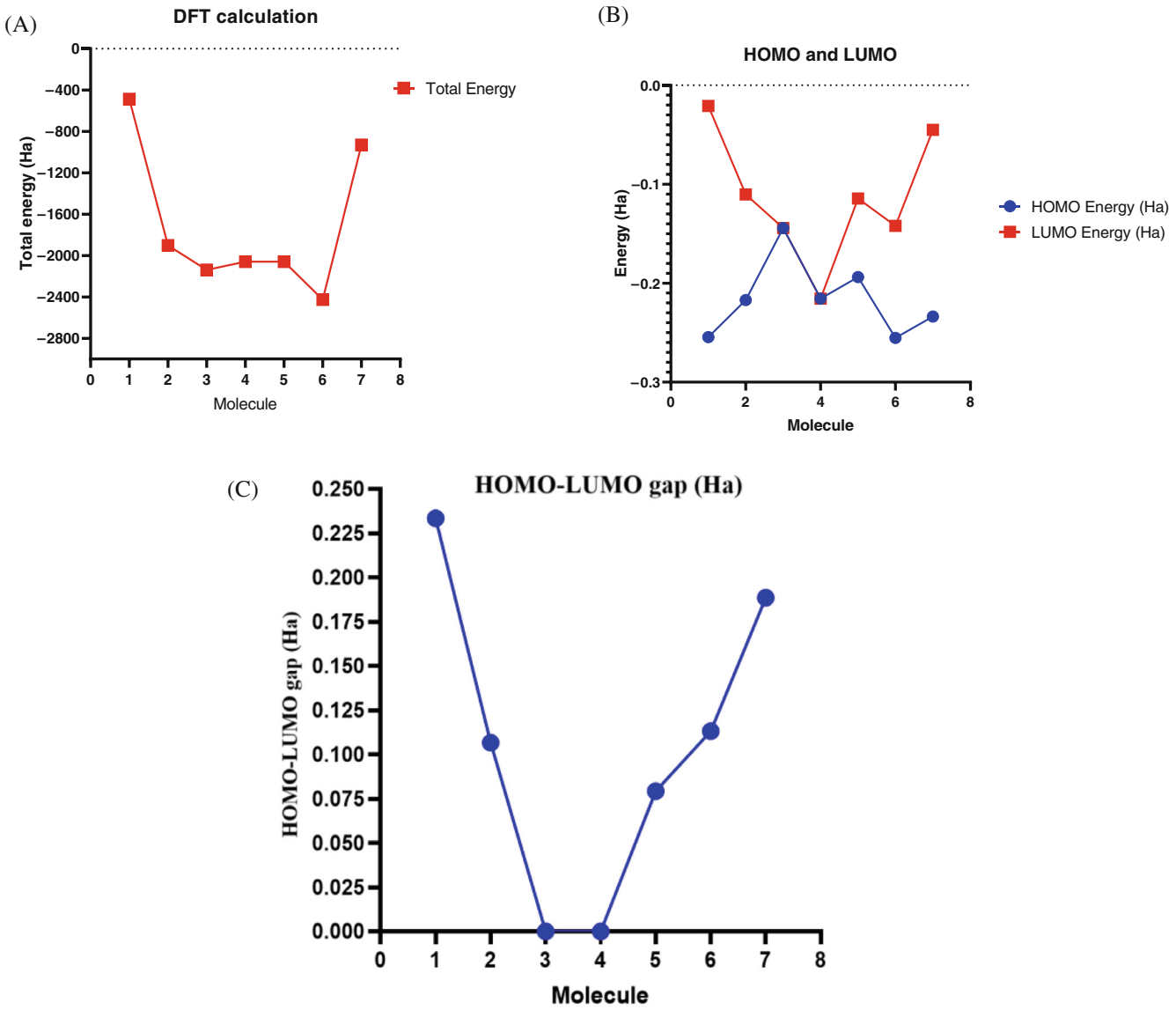


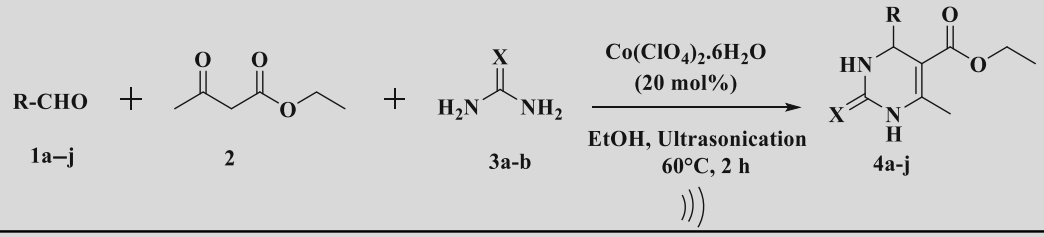
FIGURE 5 (A) Total energy (Hartree), (B) Highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy profile, and (C) HOMO–LUMO gap of seven intermediates (refer Table 4 for molecule numbers). DFT, density functional theory.

escalate the intermediates and forming the metal complex.

The developed reaction condition for DHPM synthesis using sonochemistry catalyzed by cobalt(II) perchlorate hexahydrate was explored to synthesize different derivatives, as shown in Table 5. A good to excellent yield of 67%–92% was observed in all the cases under ultrasonication in 2 h. Furthermore, aromatic aldehydes like benzaldehyde and electron-withdrawing group substituted aromatic aldehyde also gave the respective DHPMs derivatives a good yield (Entries 1–11, Table 5). Here, electron-donating group substituted derivatives also offered moderate yield (Entries 12–14, Table 5). Finally, aliphatic aldehydes like acetaldehyde and propionaldehyde were reacted with urea and EAA to yield the products **4o** and **4p** with 79% and 75%, respectively (entries 15–16, Table 5).

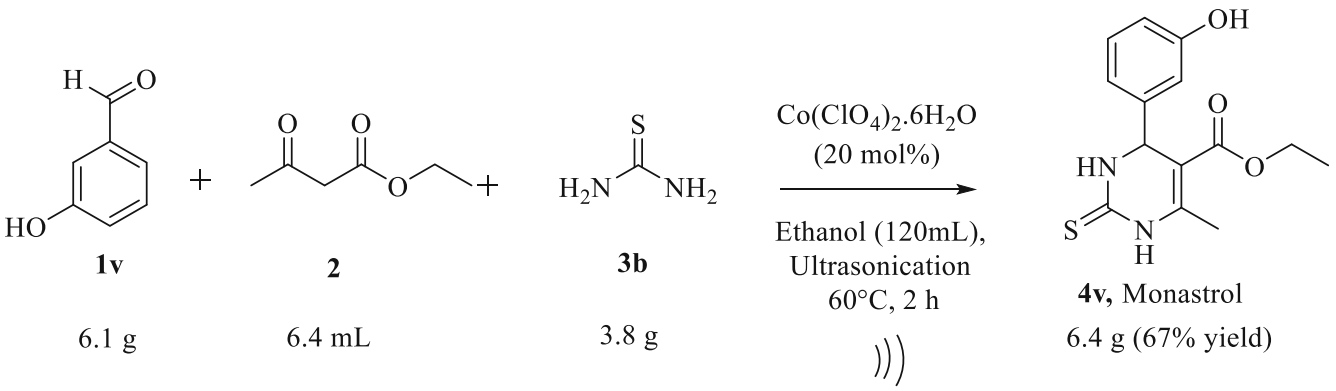
Looking at the promising results for synthesizing dihydropyrimidin-ones we further investigated the feasibility of the above method in synthesizing

TABLE 5 Synthesis of different 3,4-dihydropyrimidin-2(1H)-one (DHPMs) derivatives with $Co(ClO_4)_2{\cdot}6H_2O$ as a Lewis acid catalyst.[a]



Entry	Product	R	X	Yield[b] (%)
1	**4a**	Ph	O	92
2	**4b**	4-Br-Ph	O	80
3	**4c**	4-Cl-Ph	O	85
4	**4d**	4-CF_3-Ph	O	65
5	**4e**	4-OH-Ph	O	70
6	**4f**	4-NO_2-Ph	O	66
s7	**4g**	3-Br-Ph	O	78
8	**4h**	3-F-Ph	O	82
9	**4i**	3-OH-Ph	O	70
10	**4j**	3-Cl-Ph	O	66
11	**4k**	2-Cl-Ph	O	69
12	**4l**	4-Me-Ph	O	84
13	**4m**	4-OMe-Ph	O	83
14	**4n**	3,4-Di-OMe-Ph	O	78
15	**4o**	CH_3	O	79
16	**4p**	CH_3–CH_2–	O	75
17	**4q**	Ph	S	67
18	**4r**	4-Cl-Ph	S	65
19	**4s**	3-Br-Ph	S	66
20	**4t**	3-F-Ph	S	65
21	**4u**	4-OH-Ph	S	65
22	**4v**	3-OH-Ph	S	67
23	**4w**	4-Me-Ph	S	69
24	**4x**	4-OMe-Ph	S	65
25	**4y**	CH_3	S	65
26	**4z**	CH_3–CH_2–	S	68

[a]All reactions were performed with 2 mmol (1 equiv) of **1a–z**, **2**, and **3a–b** in 5 mL of ethanol as a solvent in the presence of 20 mol% of of $Co(ClO_4)_2{\cdot}6H_2O$ at 60°C in ultrasonication till 2 h.
[b]Isolated yields DHPM (**4a–z**).



SCHEME 1 Scale-up synthesis of monastrol.

dihydropyrimidin-thiones by reacting the aldehyde with thiourea (**3b**) and EAA (**2**). Interestingly $Co(ClO_4)_2{\cdot}6H_2O$ was found to be equally good in synthesizing a variety of dihydropyrimidin-thiones with a good yield of 65%–69% (Entries 17–26, Table 5). Again, aromatic aldehyde with a substituted electron-withdrawing group (Entries 17–22, Table 5) and electron-donating group (Entries 23 and 24, Table 3) were transformed via one-pot reaction into the thio-Biginelli products. Furthermore, aliphatic aldehydes were also transformed into the respective dihydropyrimidin- thiones in a good yield (Entries 24 and 26, Table 5).

This efficient, one-pot, and economic sonochemistry methodology was further explored in the gram-scale synthesis of monastrol (Scheme 1). Monastrol is a biologically active important DHPM derivative used as an antiproliferative agent inhibiting the kinesin-5 [16]. We used an ethanolic solution (150 mL) of 3-hydroxy benzaldehyde (6.1 g, 50 mmol), EAA (6.4 mL, 50 mmol), and thiourea (3.8 g, 50 mmol) and added $Co(ClO_4)_2{\cdot}6H_2O$ (3.24 g, 20 mol %). The solution was ultrasonicated for 2 h as the completion of the reaction. After cooling, it was poured into crushed ice to obtain the solid product recrystallized from diethyl ether to get pure monastrol (**4v**) in a good yield (6.4 g, 67%).

3 | CONCLUSION

In conclusion, we have developed a sustainable, economical, and efficient synthesis of dihydropyrimidin-ones/-thiones via a three-component Biginelli reaction using sonochemistry catalyzed by cobalt(II) perchlorate hexahydrate. We explored MS and DFT calculations to establish the cobalt-catalyzed reaction mechanism. The method showed the potential of $Co(ClO_4)_2{\cdot}6H_2O$ as a Lewis acid catalyst to promote the reaction along with sonochemistry in a one-pot to afford the different derivatives of DHPMs in good to excellent yield in less time. The developed method could be helpful in the easy and economical synthesis of drugs and drug-like molecules, exemplified by the gram-scale synthesis of monastrol.

4 | EXPERIMENTAL SECTION

All the chemicals and solvents were purchased from Sigma Aldrich, Spectrochem Pvt. Ltd., and Sisco Research Laboratories Pvt. Ltd. and used without purification. The reactions were monitored using thin-layer chromatography on Merck pre-coated silica gel plates 60 F254 (0.25 mm), and the compounds were examined under a UV chamber. JEOL RESONANCE ECZ500R was used to record ^1H and ^{13}C NMR spectra (DMSO-d_6) at 500 and 125 MHz, respectively using TMS as an internal standard. Chemical shift values were given in parts per million (ppm) scale and coupling in Hertz (Hz). Splitting patterns are described as singlet (s), doublet (d), triplet (t), multiplet (m), doublet of doublet (dd), and doublet of triplet (dt). HRMS was carried out in an ESI quadrupole time-of-flight mass spectrophotometer. The IR spectra were recorded on a BRUKER ECO-ATR Spectrometer.

4.1 | General procedure for the synthesis of dihydropyrimidin-ones and -thiones

Benzaldehyde (0.21 g, 2 mmol, 1 equiv), EAA (0.26 mL, 2 mmol, 1 equiv), and urea or thiourea (0.12 g, 2 mmol, 1 equiv) were dissolved in ethanol (5 mL) in a round bottom flask. This reaction mixture was ultrasonicated in the presence of cobalt perchlorate hexahydrate (0.129 g, 20 mol %) for 2 h. Thin-layer chromatography monitored the progress of the reaction. After completion of the

reaction, the stirring was stopped, and the reaction mass was cooled. The reaction mixture was poured into crushed ice (20 g) and stirred for 5–10 min. Finally, the solid separated was filtered under a suction pump and washed with ice-cold water. Further, the solid product was recrystallized from diethyl ether to afford the pure product (0.46 g, 92%).

4.2 | Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4a)

Yield 92% (0.46 g); white solid; mp: 216–217°C; FT-IR (cm^{-1}): 3741, 3239, 3109, 2976, 2309, 1698, 1698, 1643, 1457, 1289, 1219, 1087, 758, 698; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.19 (s, 1H), 7.73 (s, 1H), 7.31–7.26 (m, 2H), 7.20 (d, $J = 5.2$ Hz, 3H), 5.11 (s, 1H), 3.94 (dd, $J = 15.1$, 8.0 Hz, 2H), 2.21 (s, 3H), 1.06 (t, $J = 8.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.9, 152.8, 148.9, 145.4, 128.9, 127.8, 126.7, 99.7, 59.7, 54.5, 18.3, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_3$, 261.1239, found 261.1240.

4.3 | Ethyl 4-(4-bromophenyl)-6-methyl-2-oxo-1,2,3,4 tetrahydropyrimidine-5-carboxylate (4b)

Yield 80% (0.54 g); white solid; mp: 217–218°C; FT-IR (cm^{-1}): 3739, 3241, 3111, 2978, 2308, 1703, 1646, 1459, 1289, 1221, 1087, 778; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.22 (s, 1H), 7.75 (s, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 5.09 (s, 1H), 3.94 (q, $J = 7.1$ Hz, 2H), 2.21 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 165.7, 152.5, 149.3, 144.7, 131.9, 129.1, 120.9, 99.3, 59.8 53.9, 18.3, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{17}BrN_2O_3$, 339.0339, found 339.0359.

4.4 | Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4c)

Yield 85% (0.50 g); white solid; mp: 212–213°C; FT-IR (cm^{-1}): 3740, 3098, 2953, 2309, 1699, 1641, 1458, 1286, 1215, 1083, 774; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.22 (s, 1H), 7.75 (s, 1H), 7.49 (d, $J = 8.4$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 5.08 (s, 1H), 3.94 (q, $J = 7.1$ Hz, 2H), 2.21 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.7, 152.5, 149.3, 144.7, 131.9, 129.1, 120.9, 99.3, 59.8, 53.9, 18.3, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{16}ClN_2O_3$, 295.0849, found 295.0853.

4.5 | Ethyl 6-methyl-2-oxo-4-(4-(trifluoromethyl) phenyl)-1,2,3,4 tetrahydropyrimidine-carboxylate (4d)

Yield 65% (0.43 g); white solid; mp: 217–219°C; FT-IR (cm^{-1}): 3739, 3239, 3100, 2974, 2309, 1701, 1648, 1327, 1221, 1087; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.28 (s, 1H), 7.82 (s, 1H), 7.68 (d, $J = 8.2$ Hz, 2H), 7.41 (d, $J = 8.1$ Hz, 2H), 5.18 (s, 1H), 3.94 (q, $J = 7.0$ Hz, 2H), 2.22 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.7, 152.4, 149.8, 149.6, 128.7, 127.8, 126.0, 126.0, 99.0, 59.9, 54.2, 18.4, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{15}H_{16}F_3N_2O_3$, 329.1113, found 329.1119.

4.6 | Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4e)

Yield 70% (0.38 g); white solid; mp: 214–215°C; FT-IR (cm^{-1}): 3736, 3271, 3096, 2975, 2309, 1652, 1449, 1224, 1093, 793; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.32 (s, 1H), 9.10 (s, 1H), 7.61 (s, 1H), 6.98 (d, $J = 8.5$ Hz, 2H), 6.65 (d, $J = 8.5$ Hz, 2H), 5.00 (s, 1H), 3.93 (q, $J = 7.1$ Hz, 2H), 2.19 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.9, 152.7, 148.3, 135.9, 127.9, 115.5, 100.2, 59.6, 53.9, 49.1, 18.3, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_4$, 277.1188, found 277.1182.

4.7 | Ethyl 6-methyl-4-(4-nitrophenyl)-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4f)

Yield 66% (0.40 g); white solid; mp: 214–216°C; FT-IR (cm^{-1}): 3623, 3224, 3126, 2988, 2339, 1700, 1640, 1293, 1214, 1089, 771; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.34 (s, 1H), 8.18 (d, $J = 8.6$ Hz, 2H), 7.88 (s, 1H), 7.46 (d, $J = 8.6$ Hz, 2H), 5.23 (s, 1H), 3.94 (q, $J = 7.1$ Hz, 2H), 2.22 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.6, 152.5, 152.3, 149.9, 147.2, 128.2, 124.4, 98.7, 59.9, 54.2, 18.4, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{16}N_3O_5$, 306.1090, found 306.1088.

4.8 | Ethyl 4-(3-bromophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4g)

Yield 78% (0.52 g); white solid; mp: 216–218°C; FT-IR (cm^{-1}): 3742, 3432, 3160, 3016, 2353, 1813, 1708, 1658, 1587, 1474, 1330, 1233, 1122, 993, 751, 608; ^{1}H NMR

(500 MHz, DMSO-d_6): δ ppm 9.26 (s, 1H), 7.78 (s, 1H), 7.41 (d, $J = 7.9$ Hz, 1H), 7.35 (s, 1H), 7.27 (t, $J = 7.8$ Hz, 1H), 7.19 (d, $J = 7.7$ Hz, 1H), 5.10 (s, 1H), 3.95 (q, $J = 7.2$ Hz, 2H), 2.21 (s, 3H), 1.06 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 165.7, 152.4, 149.5, 148.0, 131.4, 130.7, 129.7, 125.8, 122.0, 99.1, 59.9, 54.1, 18.4, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{16}B_rN_2O_3$, 339.0344, found 339.0359.

4.9 | Ethyl 4-(3-fluorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4h)

Yield 82% (0.45 g); white solid; mp: 218–219°C; FT-IR (cm^{-1}): 3739, 3432, 3342, 3201, 2312, 1854, 1854, 1854, 1683, 1583, 1429, 1288, 1130, 919, 801, 698, 649; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.25 (s, 1H), 7.79 (s, 1H), 7.34 (dd, $J = 14.2$, 7.8 Hz, 1H), 7.04 (d, $J = 6.5$ Hz, 2H), 6.96 (d, $J = 10.1$ Hz, 1H), 5.12 (s, 1H), 3.95 (dd, $J = 7.1$, 4.0 Hz, 2H), 2.22 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.8, 163.6, 161.6, 152.5, 149.5, 148.1, 131.1, 131.0, 122.7, 114.7, 114.5, 113.6, 113.4, 99.2, 59.8, 54.1, 18.3, 14.6. HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{16}N_3O_5$, 279.1145, found 279.1141.

4.10 | Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4i)

Yield 70% (0.38 g); white solid; mp: 219–220°C; FT-IR (cm^{-1}): 3743, 3517, 3351, 3247, 1724, 1673, 1635, 1452, 1312, 1225, 1105, 775, 708; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.35 (s, 1H), 9.14 (s, 1H), 7.67 (s, 1H), 7.05 (t, $J = 8.0$ Hz, 1H), 6.63 (d, $J = 7.4$ Hz, 2H), 6.58 (d, $J = 9.9$ Hz, 1H), 5.01 (s, 1H), 3.95 (q, $J = 7.1$, 2H), 2.19 (s, 3H), 1.07 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.9, 157.8, 152.8, 148.6, 146.8, 129.8, 117.4, 114.7, 113.6, 99.9, 59.7, 54.3, 18.3, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{16}FN_2O_3$, 277.1180; found 277.1186.

4.11 | Ethyl 4-(3-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4j)

Yield 66% (0.38 g); white solid; mp: 210–212°C; FT-IR (cm^{-1}) 3695, 3210, 3094, 2927, 2316, 1702, 1648, 1473, 1425, 1283, 1223, 1086, 768, 691; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.24 (s, 1H), 7.76 (s, 1H), 7.33 (t, $J = 7.8$ Hz, 1H), 7.28 (d, $J = 8.7$ Hz, 1H), 7.21 (s, 1H), 7.16 (d, $J = 7.6$ Hz, 1H), 5.12 (s, 1H), 3.95 (q, $J = 8.2$ Hz, 2H), 2.22 (s, 3H), 1.06 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.7, 152.4, 149.5, 147.8, 133.4, 131.0, 127.8, 126.8, 125.4, 99.1, 59.8, 54.1, 18.4, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{16}ClN_2O_3$ 295.0849, found 295.0841.

4.12 | Ethyl 4-(2-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4k)

Yield 69% (0.40 g); white solid; mp: 212–214°C; FT-IR (cm^{-1}): 3717, 3233, 3097, 2936, 2313, 1701, 1641, 1438, 1220, 1078, 758, 675; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.22 (s, 1H), 7.66 (s, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.28 (d, $J = 4.1$ Hz, 2H), 7.25–7.21 (m, 1H), 5.60 (s, 1H), 3.85 (q, $J = 7.0$ Hz, 2H), 2.26 (s, 3H), 0.95 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.5, 151.9, 149.8, 142.2, 132.2, 129.9, 129.6, 129.3, 128.3, 98.4, 59.6, 51.9, 18.2, 14.4; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{16}ClN_2O_3$, 295.0849, found 295.0857.

4.13 | Ethyl 6-methyl-2-oxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4l)

Yield 84% (0.46 g); white solid; mp: 212–214°C; FT-IR (cm^{-1}): 3737, 3238, 3103, 2929, 2309, 1701, 1645, 1459, 1285, 1220, 1086, 780; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.14 (s, 1H), 7.67 (s, 1H), 7.07 (d, $J = 4.1$ Hz, 4H), 5.06 (s, 1H), 3.94 (q $J = 6.9$ Hz, 2H), 2.21 (dd, $J = 9.0$, 3.9 Hz, 6H), 1.06 (t, $J = 9.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.9, 152.7, 148.7, 142.5, 136.9, 129.4, 126.7, 99.9, 59.7, 54.1, 21.8, 18.3, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_3$, 275.1396, found 275.1391.

4.14 | Ethyl 4-(4-methoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4m)

Yield 83% (0.48 g); white solid; mp: 212–214°C; FT-IR (cm^{-1}): 3739, 3237, 3099, 2953, 2309, 1700, 1644, 1456, 1277, 1217, 1173, 1083, 1028, 779; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.15 (s, 1H), 7.67 (s, 1H), 7.11 (d, $J = 7.3$ Hz, 2H), 6.84 (d, $J = 7.3$ Hz, 2H), 5.05 (s, 1H), 3.94 (dd, $J = 14.4$, 7.0 Hz, 2H), 3.68 (s, 3H), 2.21 (s, 3H), 1.05 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.9, 158.9, 152.7, 148.7, 137.6, 128.0, 127.8, 114.2, 100.1, 59.7, 55.6, 53.9, 53.7, 18.3, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_4$ 291.1345; found, 291.1338.

4.15 | Ethyl 4-(3,4-dimethoxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4n)

Yield 78% (0.45 g); white solid; mp: 215–217°C; FT-IR (cm^{-1}): 3739, 3248, 3008, 2934, 2834, 2311, 1706, 1654, 1512, 1439, 1324, 1226, 1137, 1089, 793, 690; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 9.14 (s, 1H), 7.66 (s, 1H), 6.85 (d, $J = 8.3$ Hz, 1H), 6.80 (s, 1H), 6.68 (d, $J = 8.2$ Hz, 1H), 5.05 (s, 1H), 3.95 (q, $J = 7.0$ Hz, 2H), 3.67 (s, 6H), 2.20 (s, 3H), 1.06 (s, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.9, 152.8, 148.9, 148.7, 148.5, 137.8, 118.4, 112.2, 110.8, 99.9, 59.7, 56.0, 55.9, 53.9, 18.3, 14.7; HRMS: m/z $[M + H]^+$ calcd for $C_{16}H_{21}N_2O_5$ 321.1450, found 321.1445.

4.16 | Ethyl 4,6-dimethyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4o)

Yield 79% (0.31 g); white solid; mp: 212–214°C; FT-IR (cm^{-1}) 3745, 3236, 3103, 2977, 1698, 1447, 1323, 1283, 1224, 1097, 781; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 8.98 (s, 1H), 7.20 (s, 1H), 4.07 (q, $J = 4.7$ Hz, 1H), 4.01 (dd, $J = 17.5$, 9.1 Hz, 2H), 2.11 (s, 3H), 1.14 (t, $J = 7.1$ Hz, 3H), 1.05 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 165.9, 153.1, 148.4, 100.9, 59.6, 46.8, 23.9, 18.2, 14.8; HRMS: m/z $[M + H]^+$ calcd for $C_9H_{15}N_20_3$ 199.1083, found 199.1110.

4.17 | Ethyl 4-ethyl-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4p)

Yield 75% (0.31 g); white solid; mp: 211–213°C; FT-IR (cm^{-1}): 3746, 3242, 3115, 2982, 1702, 1643, 1473, 1332, 1230, 1093, 778; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 8.91 (s, 1H), 7.28 (s, 1H), 4.06–4.01 (m, 1H), 4.00 (dd, $J = 11.9$, 4.8 Hz, 2H), 2.12 (s, 3H), 1.41–1.33 (m, 2H), 1.14 (t, $J = 7.1$ Hz, 3H), 0.75 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 166.0, 153.4, 149.0, 99.2, 59.6, 51.9, 30.6, 18.2, 14.8, 9.04; HRMS: m/z $[M + H]^+$ calcd for $C_{10}H_{17}N_2O_3$, 213.1239, found 213.1245.

4.18 | Ethyl 6-methyl-4-phenyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4q)

Yield 67% (0.34 g); white solid, mp: 216–218°C; FT-IR (cm^{-1}): 3741, 3323, 3171, 3103, 2362, 1665, 1572, 1483, 1280, 1193, 1116, 759, 689, 650; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 10.32 (s, 1H), 9.64 (s, 1H), 7.31 (t, $J = 7.5$ Hz, 2H), 7.23 (t, $J = 7.2$ Hz, 1H), 7.18 (d, $J = 7.7$ Hz, 2H), 5.14 (s, 1H), 3.96 (q, $J = 7.0$ Hz, 2H), 2.26 (s, 3H), 1.05 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 174.7, 165.7, 145.6, 144.0, 129.1, 128.3, 126.9, 101.2, 60.2, 54.6, 17.7, 14.5. HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_2S$, 277.1011, found 277.1020.

4.19 | Ethyl 4-(4-chlorophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4r)

Yield 65% (0.38 g); white solid; mp: 213–215°C; FT-IR (cm^{-1}): 3741, 3323, 3169, 3097, 2381, 1668, 1585, 1480, 1280, 1193, 1116, 804, 745; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 10.35 (s, 1H), 9.63 (s, 1H), 7.39 (d, J = 8.5 Hz, 2H), 7.19 (d, J = 8.5 Hz, 2H), 5.12 (s, 1H), 3.97 (q, J = 7.0 Hz, 2H), 2.25 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 174.8, 165.5, 146.5, 146.1, 131.5, 131.1, 129.8, 125.9, 122.2, 100.6, 60.3, 54.1, 17.7, 14.5; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{17}ClN_2O_2S$, 311.0621, found 311.0617.

4.20 | Ethyl 4-(3-bromophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4s)

Yield 66% (0.44 g); white solid; mp: 213–215°C; FT-IR (cm^{-1}): 3741, 3299, 3176, 2975, 2382, 1652, 1557, 1458, 1189, 1110, 668; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 10.39 (s, 1H), 9.65 (s, 1H), 7.45 (d, $J = 8.9$ Hz, 1H), 7.34 (s, 1H), 7.29 (t, $J = 7.8$ Hz, 1H), 7.18 (d, $J = 7.8$ Hz, 1H), 5.14 (s, 2H), 3.98 (q, $J = 7.1$ Hz, 2H), 2.26 (s, 3H), 1.06 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 174.8, 165.6, 146.5, 146.1, 131.5, 131.1, 129.8, 125.9, 122.2, 100.6, 60.3, 54.1, 17.7, 14.5; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{17}BrN_2O_2S$ 355.0116, found 355.0116.

4.21 | Ethyl 4-(3-fluorophenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4t)

Yield 65% (0.37 g); white solid; mp: 213–215°C; FT-IR (cm^{-1}): 3855, 3741, 3319, 3172, 3099, 2361, 1657, 1585, 1459, 1333, 1283, 1188, 1111, 884, 755, 684; ^{1}H NMR (500 MHz, DMSO-d_6): δ ppm 10.37 (s, 1H), 9.66 (s, 1H), 7.37 (dd, J = 14.1, 7.9 Hz, 1H), 7.08 (t, J = 9.7 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.95 (d, J = 10.0 Hz, 1H), 5.16 (s, 1H), 3.99 (q, J = 7.0 Hz, 2H), 2.26 (s, 3H), 1.06 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm

174.9, 165.5, 163.6, 161.7, 146.7, 146.7, 146.1, 131.3, 131.2, 122.9, 115.2, 114.9, 113.7, 113.5, 100.7, 60.2, 54.0, 17.7, 14.5; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{16}FN_2O_2S$, 295.0917, found 295.0916.

4.22 | Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4u)

Yield 65% (0.35 g); white solid; mp: 215–216°C; FT-IR (cm^{-1}): 3740, 3175, 2977, 2922, 2312, 1710, 1570, 1481, 1388, 1311, 1185, 1077, 742; ^1H NMR (500 MHz, DMSO-d_6): δ ppm 10.21 (s, 1H), 9.52 (s, 1H), 9.41 (s, 1H), 6.97 (d, $J = 8.4$ Hz, 2H), 6.67 (d, $J = 8.3$ Hz, 2H), 5.01 (s, 1H), 3.95 (q, $J = 7.0$ Hz, 2H), 2.23 (s, 3H), 1.06 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.4, 165.7, 157.4, 145.1, 134.6, 128.2, 115.7, 101.6, 60.04, 54.1, 17.7, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_3S$, 293.0960, found 293.0963.

4.23 | Ethyl 4-(3-hydroxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4v)

Yield 67% (0.36 g); white solid; mp: 214–216°C; FT-IR (cm^{-1}): 3743, 3295, 3171, 2393, 2312, 1658, 1588, 1466, 1371, 1279, 1185, 1106, 743, 693; ^1H NMR (500 MHz, DMSO-d_6): δ ppm 10.27 (s, 1H), 9.58 (s, 1H), 9.43 (s, 1H), 7.08 (t, $J = 7.7$ Hz, 1H), 6.60 (dd, $J = 7.8$, 4.9 Hz, 3H), 5.05 (s, 1H), 3.97 (q, $J = 7.1$ Hz, 2H), 2.24 (s, 3H), 1.08 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 174.7, 165.7, 157.9, 145.4, 130.0, 117.5, 115.2, 113.7, 101.3, 60.1, 54.4, 17.7, 14.6; HRMS: m/z $[M + H]^+$ calcd for $C_{14}H_{17}N_2O_3S$, 293.0960, found 293.0946.

4.24 | Ethyl 6-methyl-2-thioxo-4-(p-tolyl)-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4w)

Yield 69% (0.37 g); white solid; mp: 214–216°C; FT-IR (cm^{-1}): 3760, 3319, 3167, 2978, 2312, 1667, 1571, 1458, 1327, 1280, 1174, 1114, 758, 648; 1H NMR (500 MHz, DMSO-d_6): δ ppm 10.27 (s, 1H), 9.58 (s, 1H), 7.10 (d, $J = 8.0$ Hz, 2H), 7.05 (d, $J = 8.1$ Hz, 2H), 5.09 (s, 1H), 3.96 (q, $J = 7.1$ Hz, 2H), 2.24 (s, 3H), 2.22 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 174.65, 165.67, 145.40, 141.11, 137.44, 129.59, 126.82, 101.33, 60.10, 54.24, 21.19, 17.66, 14.55. HRMS: m/z $[M + H]^+$ calcd for $C_{15}H_{19}N_2O_2S$, 291.1167, found 291.1166.

4.25 | Ethyl 4-(4-methoxyphenyl)-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4x)

Yield 65% (0.37 g); white solid; mp: 217–218°C, FT-IR (cm^{-1}): 3741, 3308, 3163, 3095, 2312, 1682, 1571, 1457, 1255, 1171, 1114, 1023, 784. ^1H NMR (500 MHz, DMSO-d_6): δ ppm 10.25 (s, 1H), 9.56 (s, 1H), 7.09 (d, $J = 8.7$ Hz, 2H), 6.86 (d, $J = 8.7$ Hz, 2H), 5.07 (s, 1H), 3.96 (q, $J = 7.1$ Hz, 2H), 3.68 (s, 3H), 2.24 (s, 3H), 1.07 (t, $J = 7.1$ Hz, 3H). ^{13}C NMR (125 MHz, DMSO-d_6) δ ppm 174.5, 165.7, 159.3, 145.3, 136.2, 128.1, 114.4, 101.5, 60.1, 55.6, 53.9, 17.6, 14.6. HRMS: m/z $[M + H]^+$ calcd for $C_{18}H_{19}N_2O_3S$, 307.1116, found 307.1109.

4.26 | Ethyl 4,6-dimethyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4y)

Yield 65% (0.25 g); white solid; mp: 213–215°C; FT-IR (cm^{-1}): 3741, 3309, 3117, 2971, 2382.13, 1649, 1577, 1454, 1368, 1334, 1288, 1186, 1118, 765, 639; ^1H NMR (500 MHz, DMSO-d_6): δ ppm 10.09 (s, 1H), 9.16 (s, 1H), 4.09 (q $J = 10.6$ Hz, 1H), 4.04 (q $J = 10.4$ Hz, 2H), 2.15 (s, 3H), 1.15 (t, $J = 7.1$ Hz, 3H), 1.05 (d, $J = 6.3$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 175.1, 165.6, 145.3, 102.4, 60.0, 47.2, 23.3, 17.6, 14.7; HRMS: m/z $[M + H]^+$ calcd for $C_9H_{15}N_2O_2S$, 215.0854, found 215.0859.

4.27 | Ethyl 4-ethyl-6-methyl-2-thioxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate (4z)

Yield 68% (0.28 g); white solid; mp: 214–216°C; FT-IR (cm − 1): 3741, 3308, 3175, 3107, 2963, 2361, 2361, 1654, 1574, 1453, 1372, 1305, 1274, 1182, 1120, 766, 655; ^1H NMR (500 MHz, DMSO-d_6): δ ppm 10.04 (s, 1H), 9.19 (s, 1H), 4.07 (q, $J = 7.1$ Hz, 1H), 4.04–4.00 (m, 2H), 2.16 (s, 3H), 1.42–1.35 (m, 2H), 1.15 (t, $J = 7.1$ Hz, 3H), 0.74 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ ppm 175.6, 165.8, 145.9, 100.5, 59.9, 52.2, 29.7, 17.60, 14.7, 8.7. HRMS: m/z $[M + H]^+$ calcd for $C_{10}H_{17}N_2O_2S$, 229.1011, found 229.1017.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supporting information of this article.

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