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ORIGINAL PAPER

One-pot Biginelli synthesis of novel series of 2-oxo/thioxo/imino-1,2,3,4-tetrahydropyrimidine based on 4-hydroxy-2-pyridone

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Abstract
An efficient multicomponent reaction was developed to synthesis of a novel series of (±)-7-methyl-4-aryl-4,6-dihydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione/thione/imine from bio-based 4-hydroxy-6-methylpyridine-2-ones, aromatic aldehydes and urea/thiourea/guanidine in the presence of $ZnCl_2.2H_2O$ in ethanol at 70 °C. Mild conditions as well as the operational simplicity, easy work up, environmentally friendly are the most advantages of this multicomponent for synthesis of potentially bioactive new products.

Keywords 1,2,3,4-Tetrahydropyrimidine · 4-Hydroxy-pyridine-2-one · Urea · Thiourea · Guanidine · $ZnCl_2{\cdot}2H_2O$ · Multicomponent reaction

Introduction

2-oxo/thioxo/imino-1,2,3,4-tetrahydropyrimidines (**THPM**s; Fig. 1) are a bunch of key heterocycle compounds introduced by an Italian chemist, Pietro Biginelli, during a one-pot reaction. **THPM** is obtained from the reaction of three components urea (thiourea), an aldehyde, and a 1,3-dicarbonyl compound (Kappe 2000). The change in three types of starting material provides a variety of THPOs that can show a wide range of biological activities, including antiviral **I** (Chitra et al. 2010; Kim et al. 2012) anticancer **II** (Mayer et al. 1999; Milović et al. 2022b), antibacterial **III** (Yadlapalli et al. 2012; Milović et al. 2022a) antifungal **IV** (Rajanarendar et al. 2010), anticancer (Ismaili et al. 2008; Janković et al. 2019) anti-inflammatory activity **V** (Gijsen et al. 2012), antioxidant agents **VI** (Ismaili et al. 2008) and Calcium channel inhibition **VII** (Ismaili et al. 2008). Due to these features, very quickly studies were conducted on **THPM**s, and almost all of the main chemistry publications contained articles about of the Biginelli reaction (Dallinger et al. 2004; Kolosov et al. 2009). Years after the discovery of **THPM**s, researchers still emphasize the introduction of new synthetic methods, the production of new **THPM**-based compounds, and their application in the industry, particularly new drug applications (Ling et al. 2021).

Although, so far, various methods for synthesizing **THPM**s have been based on using strong Lowry-Bronsted acids such as as H_2SO_4 (Folkers and Johnson 1933b), HCl (Folkers and Johnson 1933a), Lowry-Bronsted bases such as t-BuOK (Shen et al. 2010), Lewis acids such as $InCl_3$ (Ranu et al. 2000; Nebo et al. 2019), Lewis bases such as (Debache et al. 2008), metal complex (Jankovic et al. 2015) and other types of conditions such as and zeolite (Rani et al. 2001) metal triflates (Su et al. 2005), such as ultrasonic in the presence of dendrimer-attached phosphotungstic acid nanoparticles immobilized on nanosilica (Safaei-Ghomi et al. 2018), low melting acidic (Gore et al. 2011) methods and ionic liquid (Valizadeh and Shockravi 2009) media have been presented in articles, the report of the new methods with mild conditions in terms of operation simplicity, economic viability, and greater selectivity for the preparation of potentially bioactive **THPM**s is still noticeable (Fig. 2).

From the point of view of the discovery of new drugs, bio-compound screening programs can be very effective for using natural compounds as starting materials in the preparation of new drugs from the category of known drug compounds (Newman and Cragg 2007). One class of these natural compounds are 4-hydroxy-2-pyridones (**HPO**s) alkaloids (Jessen and Gademann 2010). **HPO**

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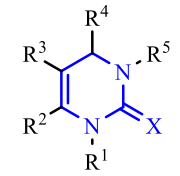


X= O, S, NH;
R$^{1\text{-}5}$= H, Alkyl, Aryl, ...

Fig. 1 Structure of Biginelli adducts

derivatives are six-membered heterocycles that are mainly produced by fungi, and cause pathogenicity or incapacitate insects and actually regulate insect behavior (Molnár et al. 2010). Most of them were isolated from fungi (Hubka et al. 2015) and some from plants (Nebo et al. 2019). These compounds have many biological activities such as antifungal (Breinholt et al. 1997) (A), antibiotic (Singh et al. 2012) (B), insecticidal (Wachira et al. 2014) (C), cytotoxic (Bergmann et al. 2007), neurotoxic (Ferraz et al. 1999), anti-proliferative (Ding et al. 2014), antibacterial (Alfatafta et al. 1994), and anti-oxidant (D) (Kamali et al. 2020).

In continuation of our previous research (Kamali and Keramat Pirolghor 2022), we wish to present an efficient one-pot multicomponent synthesis of a new series of **THPM**s using **HPO**s and aromatic aldehydes and urea/thiourea/guanidine in the presence of $ZnCl_2.2H_2O$ as the catalyst (Fig. 3).

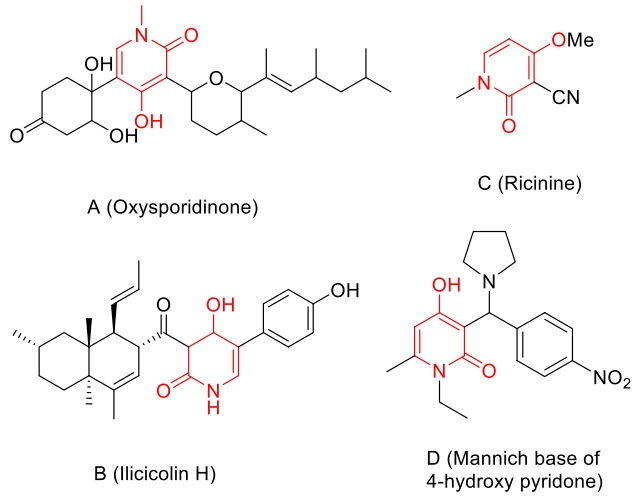


Fig. 3 Representative of some biological active 4-hydroxy-2-pyridones

Results and discussion

According to the main goal of this research, the synthesis of 4-hydroxy-2-pyridones-based **THPM**, we first treated 1-ethyl-4-hydroxy-6-methylpyridin-2-one (**1a**), benzaldehyde (**2a**) and urea (**3a**) in the presence of HCl as the catalyst in ethanol under reflux conditions (Scheme 1 and Table 1; entry 1). As a result, it was afforded **4a** (65% yield). For synthesizing of **THMP** (**5a**), this reaction was

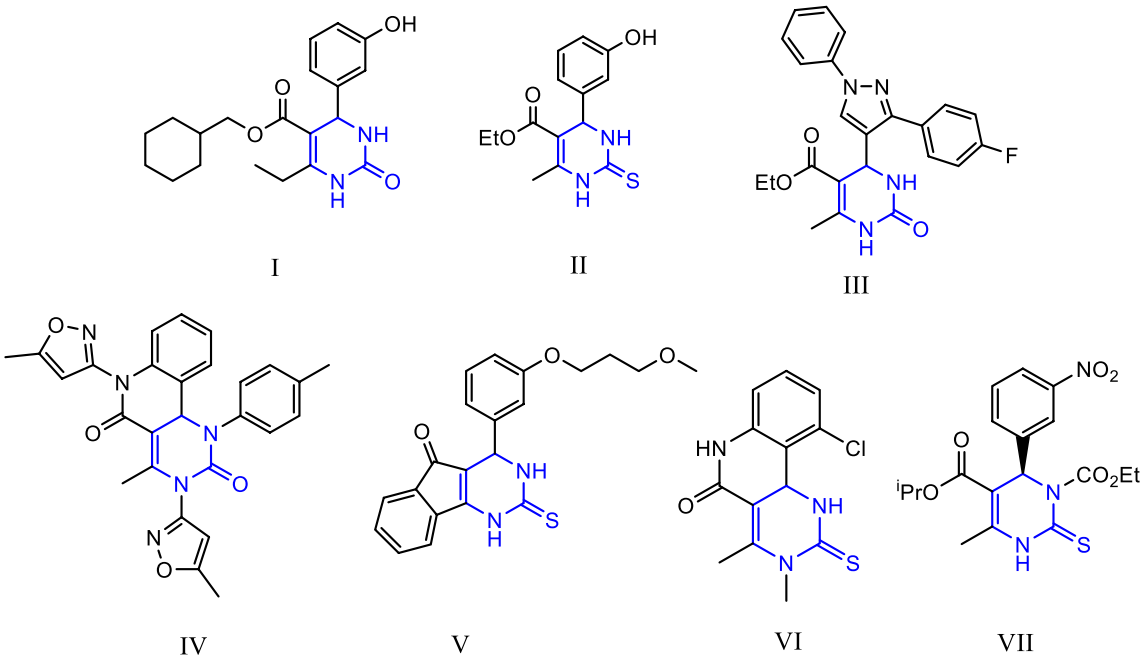
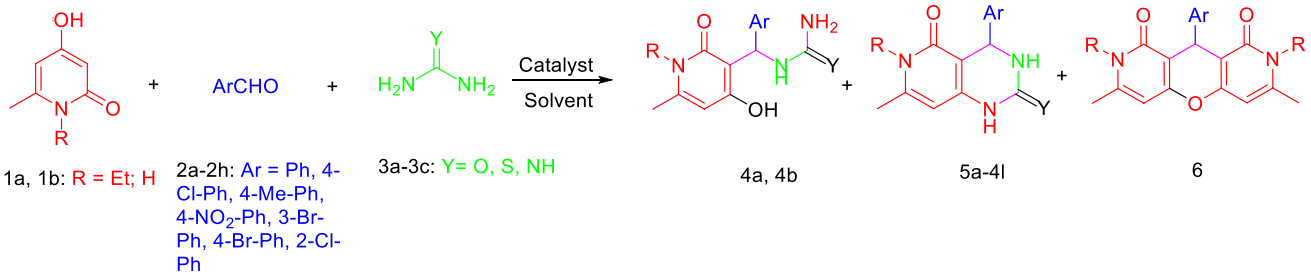


Fig. 2 Representative of some biological active THPOs



Scheme 1 Multicomponent reaction of aldehydes, 4-hydroxy-pyridine-2-ones and urea/thiourea/guanidine

Table 1 Synthesis of **THPM** (**5a** and **5b**) in the presence of different catalysts

Entry	Catalyst (mol%)	Product/Yield **4a** or **4b** (%)[a]	Product/Yield **5a** or **5b** (%)[a]
1	HCl (1 drop)	65	–
2	p-TSA (50)	83	–
3	TEA (50)	40	–
4[b]	p-TSA (50)	**87**	–
5	$SnCl_2.2H_2O$ (50)	20	63
6	–	Trace[c]	–

Reaction conditions: **1a** (1 mmol), benzaldehyde (1 mmol), urea (1 mmol) in ethanol (1 mL) at reflux in 8 h

[a]Isolated yield

[b]p-Chlorobenzaldehyde was used instead benzaldehyde

[c]Monitored by TLC

Table 2 Synthesis of **4a** and **5a** with different Lewis acid catalysts and solvents

Entry	Solvent	Catalyst (50 mol%)	Yield **4a** (%)[a]	Yield **5a** (%)[a]
1	Ethanol	$CoCl_2.H_2O$	28	51
2	**Ethanol**	**$ZnCl_2.H_2O$**	**32**	**59**
3	Ethanol	$CdCl_2.H_2O$	30	55
4	H_2O	$ZnCl_2.H_2O$	10	28
5	DMF	$ZnCl_2.H_2O$	20	32
6	THF	$ZnCl_2.H_2O$	25	38
7	Neat	$ZnCl_2.H_2O$	23	50

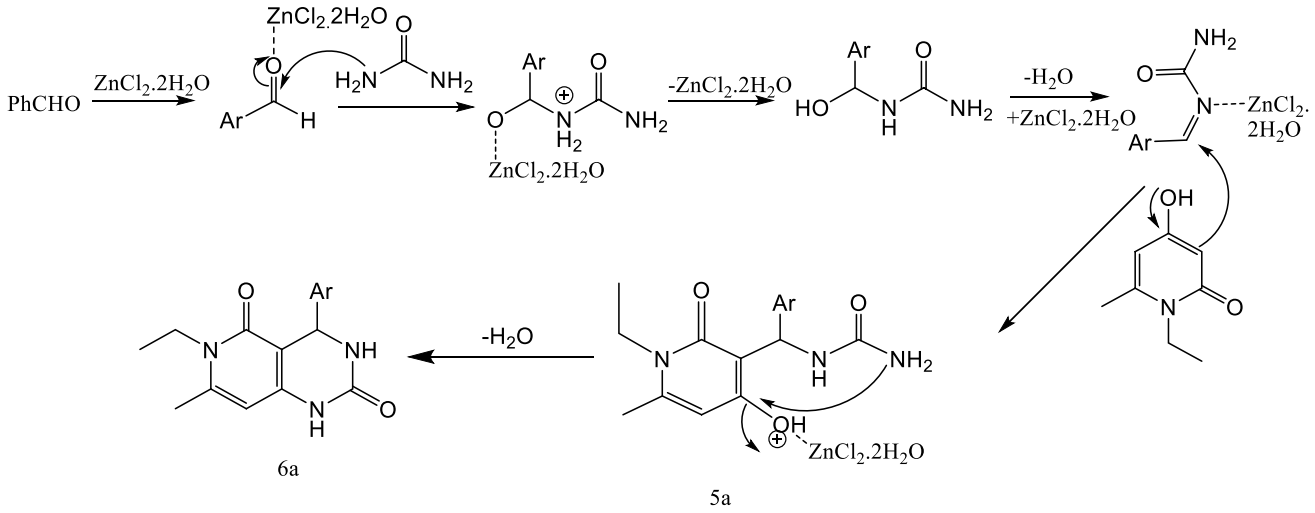
Reaction conditions: 1a (1 mmol), Benzaldehyde (1 mmol), urea (1 mmol) at reflux in 8 h

[a]Isolated yield

done in the presence of p-TSA instead of HCl (Scheme 1 and Table 1; Entry 2). In this reaction, the product **5a** was not obtained, too. We repeated this reaction in the presence of a basic catalyst (Et_3N; Table 1, Entry 3), and also with p-chlorobenzaldehyde (**2b**; Table 1, Entry 4). But **5a** or **5b** were not observed. Therefore, it was tested this reaction in the presence of $SnCl_2.2H_2O$ (based on our previous work(Kamali and Keramat Pirolghor 2022)) as Lewis acid catalysts (Table 2; Entry 5). As a result, $SnCl_2.2H_2O$ unlike to HCl or p-TSA (Brønsted-Lowry acids) and TEA (base catalyst) produced **5a** as a main product. This behavior is probably due to the effect of tin chloride in the accumulation of substrates, and iminium intermediate, which provides a better catalytic role, and also causes dehydration in the last step of the reaction (Scheme 2) (Kamali and Keramat Pirolghor 2022). So we turned to some other metal chlorides (Table 2; Entry 1–3) to optimize the reaction conditions, and also performed a reaction without of any catalyst for a more investigation (Table 1; Entry 6). The $SnCl_2.2H_2O$ gave better yield product (63%) than the other metal chloride salts (Table 2; Entry 1–3). But, because of more eco-friendly, $ZnCl_2.2H_2O$ with slightly lower product yield (59%) than $SnCl_2.2H_2O$ was selected as main catalyst for this reaction.

For optimization of other reaction condition, the reaction was performed in some other solvents (Table 2; Entry 4–7), different amounts of catalyst (Table 1; Entry 4 and Table 3; Entry 1–3), different temperatures and times (Table 3; Entry 4–9). Consequently, the best amount of catalyst, solvent type, temperature and time of reaction for synthesis of **5a** with 83% yield were 20 mol%, ethanol, 70 °C and 3 h, respectively. This reaction was economic and environmental friendly.

To further investigations and extend the library synthesis of **THPM**, some aromatic aldehydes (**2a–2h**) with electron withdrawing or donating groups, two 2-pyridones (**1a, 1b**) and urea/thiourea/guanidine (**3a–3b**) were treated to give the **THPM**s (**5a–5l**) in good to excellent yields (Scheme 1 and Table 4). It was seen that aldehydes with donor groups, didn't afford the **THPM**s and the bis-product such as **6** (Table 4, Entry 15, in the presence of urea) were produced. This is probably due to that the reaction goes forward from other pathway (in compare to proposed mechanism; Scheme 2) (Kamali et al. 2020) in which first one pyridone molecule interact with an aldehyde, and the knoevenagel reaction occurs, and then the second pyridone molecule be added to knoevenagel intermediate and produces product **4**. It should also be mentioned that the aldehydes having the strong acceptor groups such as **NO_2**, the better reacts to urea/thiourea/guanidine, and as



Scheme 2 Proposed mechanism

Table 3 Synthesis of **5a** with different amounts of catalyst, times and temperature's reaction

Entry	$ZnCl_2{\cdot}2H_2O$ (mol%)	Tem. (°C)	Time (h)	Yield **5a** (%)[a]
1	30	Reflux	8	68
2	20	Reflux	8	68
3	10	Reflux	8	60
4	20	70	8	81
5	20	60	8	73
6	20	70	7	81
7	20	70	4	81
8	**20**	**70**	**3**	**81**
9	20	70	2	51

Reaction conditions: 1a (1 mmol), benzaldehyde (1 mmol), urea (1 mmol) and $ZnCl_2{\cdot}2H_2O$ in ethanol

[a]Isolated yield

a result, **THPM** are obtained with more yield (Table 4, **5c**, **5i** and **5l**). Also, the reaction with this method, in the presence of aliphatic aldehydes (formaldehyde, acetaldehyde and butyraldehyde) instead of aromatic aldehydes did not produce **THPM**. At last, generally, the yield of **THPMs** were lower using pyridone **1b** than **1a** (Table 4, **5h**–**5l**), this is probably due to the more aromatic property and less acidic character of alpha hydrogen of carbonyl of **1b** which itself is a result of the tautomerization of the carbonyl group and NH (Hejazi et al. 2016) (2-Hydroxypyridine/2-Pyridone; Scheme 3).

Experimental section

The 4-hydroxy-6-methylpyridine-2-ones were synthesized according to known method (Kraus et al. 2016). The other starting materials were purchased from Merck and Fluka chemical companies. Melting points were determined with a Branstead Electrothermal model 9200 apparatus and are uncorrected. IR spectra were recorded on a Perkin Elmer RX1 Fourier transform infrared spectrometer. The ^1H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Bruker Avance 300 MHz spectrometers. Elemental analyses were carried out by a Perkin Elmer 2400 series II CHN/O analyzer.

Synthesis of 5a as a general procedure

The 1-ethyl-4-hydroxy-6-methylpyridine-2-one (1 mmol), the benzaldehyde (1 mmol) and the urea (1 mmol) were added to a solution of $ZnCl_2.2H_2O$ (20 mol%) in absolute ethanol (1 mL), and the mixture was stirred at 70 ℃ for 3 h. Then the reaction mixture was poured in ice water (5 mL) and the precipitated was collected by filtration, washed with distilled water (5 mL). The resulting product was recrystallized from DMF/H_2O (1 mL; V/V = 2:1) to give the pure **5a** as White solid in 81% yield; m.p.: 188–190 °C. Compounds **4a**–**4b**, **5b**–**5l** and **6** were obtained in the same way. Only in the cases of **4a** and **4b** products, p-TSA (50 mol%) was used instead $ZnCl_2.2H_2O$ and for isolation of them, after washing with water, the precipitate was added to ethanol 95% (5 mL), stirred for 0.5 h, and filtered. The filtrate solution was evaporated, and the solid recrystallized from ethanol 95%/water (4 mL; v/v = 3:1). The physical properties of products are in

Table 4 Synthesized of **THPM** derivatives (**5a**–**5l**), (**4a**, **4b**) and **6**

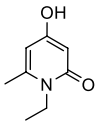
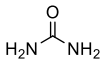
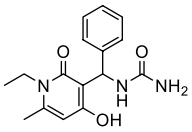
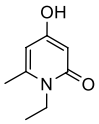
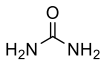
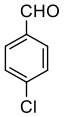
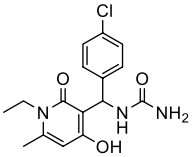
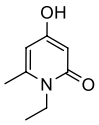
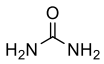
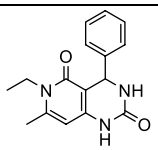
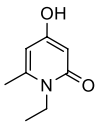
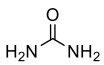
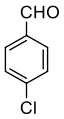
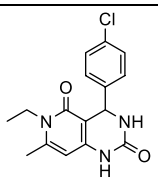
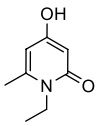
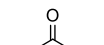
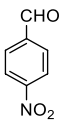
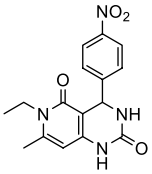
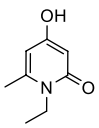
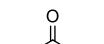
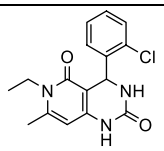
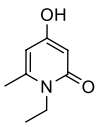
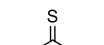
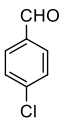
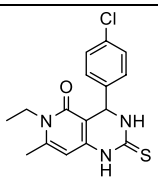
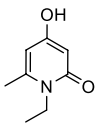
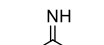
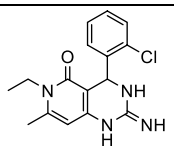
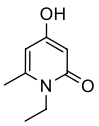
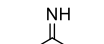
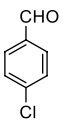
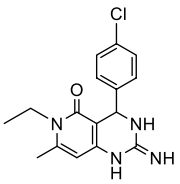
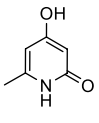
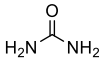
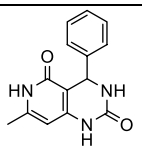
Entry	Pyridone	Urea/Thiourea /Guanidine	Aldehyde	Product name	Product	Yield%
1				**4a**		83
2				**4b**		87
3				**5a**		81
4				**5b**		86
5				**5c**		92
6				**5d**		78
7				**5e**		65
8				**5f**		78
9				**5g**		87
10				**5h**		61

Table 4 (continued)

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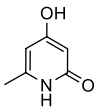
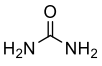
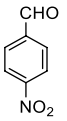
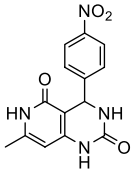
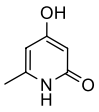
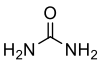
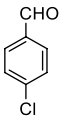
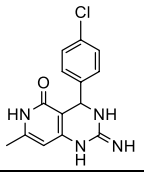
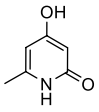
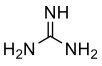
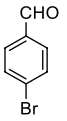
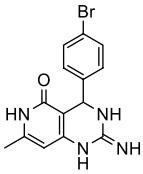
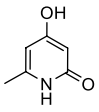
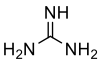
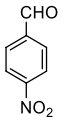
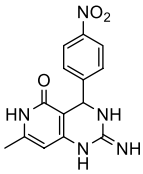
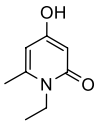
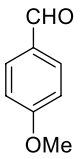
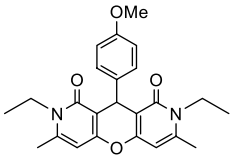
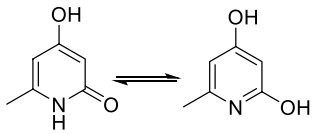
11				**5i**		85
12				**5j**		68
13				**5k**		84
14				**5l**		90
15		-		**6**		56



Scheme 3 Tautomerization of 4-hydrxoy-2-pyridone **1b**

below, and the ^{1}H NMR, ^{13}C NMR, and IR spectra attached in the Supporting Information.

(±)**-1-((1-ethyl-4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)(phenyl)methyl)urea (4a)** White solid in 83% yield; m.p.: 228–230 °C; IR (KBr) υ: 3336 (NH), 3204 (NH), 2983 (CH), 2038 (CH), 1647 (C=O cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.53 (s, 1H, OH of pyridone), 7.38–7.14 (m, 5H, ArH), 7.11 (d, J = 7.2 Hz, 1H, NH of urea), 6.24 (d, J = 7.2 Hz, 1H, CH residue of CHO), 5.87 (s, 1H, CH of pyridone), 5.81 (s, 2H, NH_2 of urea), 3.88 (2dq, J = 13.6, 6.8 Hz, 2H, CH_2 of pyridone), 2.29 (s, 3H, CH_3 of pyridone), 1.10 (t, J = 6.9 Hz, 3H, CH_3 pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.7 (=C–OH of pyrdone), 160.8 (C=O of urea), 158.1 (N–C=O of pyridone), 145.2 (=C–N of pyridone), 144.7 (C of ArH), 127.5 (CH of ArH), 126.1 (CH of ArH), 125.8 (CH of ArH), 109.1 (=CH of pyridone), 99.5 (=C of pyridone), 46.9 (CH residue of CHO), 19.5 (CH_2 of pyridone), 13.8 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{16}H_{19}N_3O_3$ (301.14): C, 63.77; H, 6.36; N, 13.94. Found: C, 63.64; H, 6.36; N, 14.08.

(±)**-1-((4-chlorophenyl)(1-ethyl-4-hydroxy-6-methyl-2-oxo-1,2-dihydropyridin-3-yl)methyl)urea (4b)** White solid in 87% yield; m.p.: 199–200 °C; IR (KBr) υ: 3345 (NH), 3196 (NH), 2989 (CH), 1647 (C=O) cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.62 (s, 1H, OH of pyridone), 7.23–7.27 (m, 4H, CH of ArH), 7.13 (d, J = 7.2 Hz, 1H, NH of urea), 6.21 (d, J = 7.2 Hz, 1H, residue CH of CHO), 5.87 (s, 1H, CH of pyridone), 5.84 (s, 2H, NH_2 of urea), 3.88 (2dq, J = 13.6, 7.0 Hz, 2H, CH_2 of pyridone), 2.29 (s, 3H, CH_3 of pyridone), 1.10 (t, J = 7.0 Hz, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.7 (=C–OH of pyridone), 161.0 (C=O of urea), 158.1 (C=O of pyridone), 145.5 (=C–N of pyridone), 143.8 (C of ArH), 130.2 (C of ArH), 127.6 (CH of ArH), 127.5 (CH of ArH), 108.7 (=CH of pyridone), 99.5 (=C of pyridone), 46.6 (CH residue of CHO), 35.8 (CH_2 of pyridone), 19.6 (CH_3 of pyridone),

13.9 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{16}H_{18}ClN_3O_3$ (335.10): C, 57.23; H, 5.40; N, 12.51. Found: C, 57.09; H, 5.31; N, 12.83.

(±)-6-ethyl-7-methyl-4-phenyl-4,6-dihydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (5a) White solid in 81% yield; m.p.: 188–190 °C; IR (KBr) υ:3341 (NH), 3196 (NH), 2956 (CH), 1661 (C=O) cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.33 (s, 1H, NH of pyrimidine), 7.57 (d, J = 7.6 Hz, 1H, NH of pyrimidine), 7.14–7.18 (m, 5H, CH of ArH), 6.39 (d, J = 7.6 Hz, 1H, CH of pyrimidine), 5.69 (s, H, CH of pyridone), 3.83–3.97 (m, 2H, CH_2 of pyridone), 2.29 (s, 3H, CH_3 of pyridone), 1.03 (t, J = 9.2 Hz, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.6 (C=O pyridone), 160.2 (C=O of pyrimidine), 154.2 (N–C= of pyridone), 147.3 (C of ArH), 144.8 (=C–NH of pyridone), 127.6 (CH of ArH), 126.0 (CH of ArH), 124.3 (CH of ArH), 106.6 (=CH of pyridone), 98.0 (=C of pyridone), 48.6 (CH of pyrimidine), 34.0 (CH of pyridone), 17.6 (CH_3 of pyridone), 11.2 (CH_3 of pyridone). Anal. Calcd for $C_{16}H_{17}N_3O_2$ (283.13): C, 67.83; H, 6.05; N, 14.83. Found: C, 67.71; H, 5.94; N, 14.94.

(±)-4-(4-chlorophenyl)-6-ethyl-7-methyl-4,6-dihydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (5b) White solid in 86% yield; m.p.: 180–182 °C; IR (KBr) υ: 3346 (NH), 3207 (NH), 2969 (CH), 2942 (CH), 1658 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.08 (s, 1H, NH of pyrimidine), 7.58 (d, J = 7.7 Hz, 1H, NH of pyrimidine), 7.25 (d, 2H, J = 7.9 Hz, CH of ArH), 7.18 (d, 2H, J = 7.9 Hz, CH of ArH), 6.32 (d, J = 7.7 Hz, 1H, CH of pyrimidine), 5.72 (s, H, CH of pyridone), 3.85–39.98 (m, 2H, CH_2 of pyridone), 2.24 (s, 3H, CH_3 of pyridone), 1.03 (t, J = 9.2 Hz, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.8 (C=O of pyrimidine), 161.0 (C=O pyridone), 155.0 (N–C of pyridone), 145.6 (C of ArH), 142.3 (C of ArH), 130.7 (=C–N of pyridone), 129.9 (CH of ArH), 127.8 (CH of ArH), 106.4 (=CH of pyridone), 98.3 (=C of pyridone), 48.6 (CH of pyrimidine), 34.0 (CH of pyridone), 19.2 (CH_3 of pyridone), 14.1 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{16}H_{16}ClN_3O_2$ (317.09): C, 60.48; H, 5.08; N, 13.22. Found: C, 60.39; H, 4.96; N, 13.34.

(±)-6-ethyl-7-methyl-4-(4-nitrophenyl)-4,6-dihydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (5c) Yellow solid in 92% yield; m.p.: 183–185 °C; IR (KBr) υ: 3304 (NH), 3190 (NH), 2992 (CH), 2943 (CH), 1642 (C=O cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.68 (s, 1H, NH of pyrimidine), 8.08 (d, J = 8.0 Hz, 2H, CH of ArH), 7.69 (d, J = 7.6 Hz, 1H, NH of pyrimidine), 7.47 (d, J = 8.0 Hz, 2H, CH of ArH), 6.35 (d, J = 7.6 Hz, 1H, CH of pyrimidine), 5.86 (s, H, CH of pyridone), 3.90 (m, 2H, CH_2 of pyridone), 2.30 (s, 3H, CH_3 of pyridone), 1.12 (t, J = 9.2 Hz, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.4 (C=O pyridone), 161.3 (C=O of pyrimidine), 153.6 (N–C= of pyridone), 145.7 (C of ArH), 137.5 (C of ArH), 127.0 (=C–NH of pyridone), 126.9 (CH of ArH), 122.9 (CH of ArH), 108.2 (=CH of pyridone), 99.3 (=C of pyridone), 47.6 (CH of pyrimidine), 35.7 (CH of pyridone), 19.6 (CH_3 of pyridone), 13.8 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{16}H_{16}N_4O_4$ (328.12): C, 58.53; H, 4.91; N, 17.06. Found: C, 58.40; H, 4.81; N, 17.21.

(±)-4-(2-chlorophenyl)-6-ethyl-7-methyl-4,6-dihydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (5d) White solid in 78% yield; m.p.: 184–185 °C; IR (KBr) υ: 336 (NH), 3067 (CH), 3158 (NH), 2988 (CH), 1646 (C=O), cm^{-1}, ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.39 (s, 1H, NH of pyrimidine), 7.67 (d, J = 7.5 Hz, 1H, NH of pyrimidine), 7.08–7.29 (m, 4H, CH of ArH), 6.28 (d, J = 7.5 Hz, 1H, CH of pyrimidine) 5.76 (s, 1H, CH of pyridone), 3.93 (dq, J = 13.1, 7.0 Hz, 1H, CH_2 of pyridone), 3.74 (dq, J = 13.1, 7.0 Hz, 1H, CH_2 of pyridone), 2.26 (s, 3H, CH_3 of pyridone), 1.10 (t, J = 7.0 Hz, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 162.7 (C=O of pyridone), 162.5 (C=O of pyrimidine), 161.6 (N–C= of pyridone), 157.8 (C of ArH), 156.3 (=C–N of pyridone), 145.3 (C of ArH), 141.3 (CH of ArH), 131.7 (CH of ArH), 128.6 (CH of ArH), 125.5 (CH of ArH), 107.2 (=CH of pyridone), 99.5 (=C of pyridone), 47.1 (CH of pyrimidine), 35.8 (CH_3 of pyridone), 19.6 (CH_3 of pyridone),14.0 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{16}H_{16}ClN_3O_2$ (317.09): C, 60.48; H, 5.08; N, 13.22. Found: C, 60.32; H, 4.95; N, 13.41.

(±)-4-(4-chlorophenyl)-6-ethyl-7-methyl-2-thioxo-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one (5e) White solid in 65% yield; m.p.: 187–189 °C; IR (KBr) υ: 3294 (NH), 3161 (CH), 2983 (CH), 1640 (C=O), 1090 (C=S) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 10.61 (s, 1H, NH of pyrimidine), 7.22 (d, J = 6.9 Hz, 2H, CH of ArH), 7.13 (d, J = 6.0 Hz, 1H, NH of pyrimidine), 6.94 (d, J = 6.9 Hz, 2H, CH of ArH), 6.10 (d, J = 6.0 Hz, 1H, CH of pyrimidine), 5.91 (s, 1H, CH of pyridone), 3.91 (m, 2H, CH_2 of pyridone), 2.31 (s, 3H, CH_3 of pyridone), 1.11 (t, J = 6.0 Hz, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 182.5 (C=S of pyrimidine), 162.2 (C=O of pyridone), 161.2 (=C–NH of pyridone), 145.5 (=C of pyridone), 143.4 (C of ArH), 128.5 (C of ArH), 127.6 (CH of ArH), 126.1 (CH of ArH), 107.93 (=C of pyridone), 99.6 (CH of pyridone), 52.3 (CH of pyrimidine), 35.4 (CH_2 of pyridone), 19.5 (CH_3 of pyridone), 13.7 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{16}H_{16}ClN_3OS$ (333.07): C, 57.57; H, 4.83; N, 12.59. Found: C, 57.39; H, 4.60; N, 12.73.

(±)-4-(2-chlorophenyl)-6-ethyl-2-imino-7-methyl-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one (5f) White solid in 78% yield; m.p.: 231–233 °C; IR (KBr) υ: 3324 (NH), 3140 (CH), 2978 (CH), 1640 (C=O). cm^{-1} .^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.53 (s, 1H, NH of pyrimidine), 7.37 (s, 1H, =NH of pyrimidine), 7.13–7.26 (m, 4H, CH of ArH), 6.98 (d, J = 6.9 Hz, 1H, NH of pyrimidone), 6.23 (d, J = 6.9 Hz, 1H, CH of pyrimidone), 5.96 (s, 1H,

CH of pyridone), 3.91 (m, 2H, CH_2 of pyridone), 2.33 (s, 3H, CH_3 of pyridone), 1.09 (t, J = 7.2 Hz, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.4 (C=O of pyridone), 162.3 (=C–NH of pyridone), 164.0 (C=NH of pyrimidine), 144.9 (=C–N of pyridone), 138.7 (C of ArH), 130.7 (C of ArH), 130.0 (CH of ArH), 129.5 (CH of ArH), 127.2 (C of ArH), 126.2 (CH of ArH), 108.8 (=C of pyridone), 99.8 (CH of pyridone), 46.2 (CH of pyrimidine), 34.5 (CH_2 of pyridone), 19.3 (CH_3 of pyridone), 13.6 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{16}H_{17}ClN_4O$ (316.11): C, 60.66; H, 5.41; N, 17.69. Found: C, 60.41, H, 5.32, N, 17.83.

(±)**-4-(4-chlorophenyl)-6-ethyl-2-imino-7-methyl-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one (5g)** White solid in 87% yield; m.p.: 209–210 °C;; IR (KBr) υ: 3305 (NH), 3194 (NH), 3082 (CH), 2922 (CH), 1646 (C=O). cm^{-1} .^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.97 (s, 1H, NH of pyrimidine), 7.78 (s, 1H, NH of pyrimidine), 7.26 (d, J = 7.25, 2H, CH of ArH), 7.24 (d, 1H, J = 6.96 Hz, = NH of pyrimidine), 6.94 (d, J = 6.96 Hz, 2H, CH of ArH), 6.13 (d, 1H, J = 6.96 Hz, CH of pyrimidine), 5.96 (s, 1H, CH of pyridone), 3.95 (m, 2H, CH_2 of pyridone), 2.37 (s, 3H, CH_3 of pyridone), 1.13 (t, J = 7.1 Hz, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.8 (C=O of pyridone), 164.4 (=C–NH of pyridone), 159.2 (NH=C of pyrimidine), 145.6 (=C–N of pyridone), 138.0 (C of ArH), 129.8 (C of ArH), 128.1 (CH of ArH), 127.7 (CH of ArH), 109.8 (=C of pyridone), 103.3 (=C of pyridone), 45.2 (CH of pyrimidine), 35.0 (CH_2 of pyridone), 19.2 (CH_3 of pyridone), 13.6 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{16}H_{17}ClN_4O$ (316.11): C, 60.66; H, 5.41; N, 17.69. Found: C, 60.41; H, 5.32; N, 17.83.

(±)**-7-methyl-4-phenyl-4,6-dihydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (5h)** White solid in 61% yield; m.p.: 275–277 °C; IR (KBr) υ: 3376 (NH), 3286 (NH), 3058 (CH), 1616 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.19 (s, 1H, NH of pyridone), 10.48 (s, 1H, NH of pyrimidine), 7.93 (d, J = 8.6 Hz, 1H, NH of pyrimidine), 7.17–7.29 (m, 5H, CHs of ArH), 6.19 (d, J = 8.6 Hz, 1H, CH of primidine), 5.72 (s, 1H, CH of pyridine), 2.05 (s, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.6 (C=O of pyridone), 162.1 (=C–NH of pyridone), 156.8 (O=C of pyrimidine), 145.0 (=C–NH of pyridone), 144.4 (C of ArH), 128.1 (CH of ArH), 127.7 (CH of ArH), 126.1 (CH of ArH), 107.9 (=C of pyridone), 96.1 (=C of pyridone), 50.0 (CH of pyrimidine), 18.3 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{14}H_{13}N_3O_2$ (255.10): C, 65.87; H, 5.13; N, 16.46. Found: C, 65.71; H, 4.98; N, 16.57.

(±)**-7-methyl-4-(4-nitrophenyl)-4,6-dihydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (5i)** Yellow solid in 85% yield; m.p.: 209–211 °C; IR (KBr) υ: 3359 (NH), 3263 (NH), 3048 (CH), 1616 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.13 (s, 1H, NH of pyridone), 10.70 (s, 1H, NH of pyrimidine), 8.12 (d, J = 8.0 Hz, 2H, CH of ArH), 7.66 (d, J = 7.7 Hz, 1H, NH of pyrimidine), 7.49 (d, J = 8.0 Hz, 2H, CH of ArH), 6.30 (d, J = 7.7 Hz, 1H, CH of pyrimidine), 5.74 (s, 1H, CH of pyridone), 2.07 (s, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.1 (C=O of pyridone), 162.0 (=C–NH of pyridone), 156.9 (O=C of pyrimidine), 152.0 (C of ArH), 151.8 (C of ArH), 147.0 (=C of pyridone), 129.5 (CH of ArH), 123.2 (CH of ArH), 108.7 (=C of pyridone), 106.6 (=C of pyridone), 49.9 (CH of pyrimidine), 18.2 (CH_3 of pyridone) ppm. Anal. Calcd for $C_{14}H_{12}N_4O_4$ (300.09): C, 56.00; H, 4.03; N, 18.66. Found: C, 55.87; H, 3.91; C, 18.81.

(±)**-4-(4-chlorophenyl)-7-methyl-4,6-dihydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (5j)** White solid in 68% yield; m.p.: 204–206 °C; IR (KBr) υ: 3359 (NH), 3267 (NH), 2924 (CH), 1620 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.08 (s, 1H, NH of pyridone), 10.72 (s, 1H, NH of pyrimidine), 7.55 (d, J = 7.6 Hz, 1H, NH of pyrimidine), 7.25 (d, br, 4H, CHs of ArH), 6.16 (d, J = 7.6 Hz, 1H, CH of pyrimidine), 5.77 (s, 1H, CH of pyridone), 2.06 (s, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 163.7 (C=O of pyridone), 163.0 (=C–NH of pyridone), 156.8 (O=C of pyrimidine), 145.7 (=C–NH of pyridone), 143.4 (C of ArH), 132.4 (C of ArH), 129.9 (CH of ArH), 127.7 (CH of ArH), 113.4 (=C of pyridone), 107.4 (=C of pyridone), 49.9 (CH of pyrimidine), 18.3 (CH_3 of pyridone) ppm. Anal. Calcd for: $C_{14}H_{12}ClN_3O_2$ (289.06): C, 58.04; H, 4.18; N, 14.50. Found: C, 58.17; H, 4.01; N, 14.69.

(±)**-4-(4-bromophenyl)-7-methyl-4,6-dihydropyrido[4,3-*d*]pyrimidine-2,5(1*H*,3*H*)-dione (5k)** White solid in 84% yield; m.p.: 208–210 °C; IR (KBr) υ: 3356 (NH), 3110 (CH), 3077 (CH), 2932 (CH), 1619 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.13 (s, 1H, NH of pyridone), 10.69 (s, 1H, NH of pyrimidine), 7.54 (d, J = 7.58 Hz, 1H, NH of pyrimidine), 7.36 (d, J = 7.52 Hz, 2H, CH of ArH), 7.21 (d, J = 7.52 Hz, 2H, CH of ArH), 6.15 (d, J = 7.58 Hz, 1H, CH of pyrimidine), 5.73 (s, 1H, CH of pyridone), 2.05 (s, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.0 (C=O of pyridone), 162.5 (=C–NH of pyridone), 157.0 (C=O of pyrimidine), 144.9 (=C–NH of pyridone), 143.7 (C of ArH), 130.5 (CH of ArH), 128.1 (CH of ArH), 122.4 (C of ArH), 112.7 (=C of pyridone), 107.9 (=C of pyridone), 47.8 (CH of pyrimidine), 19.6 (CH_3 of pyridone)Anal. Calcd for: $C_{14}H_{12}BrN_3O_2$ (333.01): C, 50.32; H, 3.62; N, 12.57. Found: C, 50.17; H, 3.62; N, 12.73.

(±)**-2-imino-7-methyl-4-(4-nitrophenyl)-2,3,4,6-tetrahydropyrido[4,3-*d*]pyrimidin-5(1*H*)-one (5l) y**ellow solid in 90% yield; m.p.: 256–258 °C; IR (KBr) υ: 3328 (NH), 3312 (NH), 2952 (CH), 3077 (CH), 2932 (CH), 1657 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.21 (s, 1H, NH of pyridone), 10.86 (s, 1H, NH of pyrimidone), 8.37 (d, J = 7.5 Hz, 1H, CH of ArH), 7.58 (d, J = 7.1 Hz,

1H, NH of pyrimidine), 7.53 (s, 1H, NH of pyrimidine), 7.30 (d, $J=7.5$ Hz, 2H, CH of ArH), 6.46 (d, $J=7.1$ Hz, 1H, CH of pyrimidine), 5.97 (s, 1H, CH of pyridone), 2.21 (s, 3H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 164.1 (C=O of pyridone), 162.0 (=C–NH of pyridone), 157.0 (NH=C of pyrimidine), 152.0 (=C–NH of pyridone), 151.8 (C of ArH), 146.0 (C of ArH), 129.5 (CH of ArH), 123.2 (CH of ArH), 114.1 (=C of pyridone), 106.6 (=C of pyridone), 48.4 (CH of pyrimidine), 19.6 (CH_3 of pyridone). Anal. Calcd for: $C_{14}H_{13}N_5O_3$ (299.10): C, 56.18; H, 4.38; N, 23.40. Found: C, 56.01; H, 4.29, N, 23.57.

2,8-diethyl-10-(4-methoxyphenyl)-3,7-dimethyl-8,10-dihydro-1*H*-pyrano[3,2-*c*:5,6-*c'*]dipyridine-1,9(2*H*)-dione (6) White solid in 56% yield; m.p.: 228–229 °C; IR (KBr) υ: 3076 (CH), 2975 (CH), 1638 (C=O) cm^{-1}. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 6.75–6.84 (m, 4H, CH of ArH), 6.05 (s, 2H, CH of pyridone), 5.89 (s, 1H, CH residue of CHO), 3.91–3.98 (m, 2H, CH_2 of pyridone), 3.68 (s, 3H, CH_3 of aldehyede), 2.36 (s, 6H, CH_3 of pyridone), 1.12 (t, $J=6.2$ Hz, 6H, CH_3 of pyridone) ppm. ^{13}C NMR (75 MHz, DMSO-d_6) δ: 168.9 ((=C of pyridone), 155.2 (C=O of pyridone), 154.2 (C-N of ArH),145.7 (=C of pyridone), 137.0 (C of ArH), 130.7 (CH of ArH), 114.1 (CH of ArH), 105.2 (=C of pyridone), 97.6 (=C of pyridone), 54.8 (O-CH_3), 50.0 (CH of pyran), 48.7 (CH_2 of pyridone), 20.3 (CH_3 of pyridone), 13.7 (CH_3 of pyridone).Anal. Calcd for: $C_{24}H_{26}N_2O_4$ (406.19): C, 70.92; H, 6.45; N, 6.89. Found: C, 70.73; H, 6.21; N, 6.61.

Conclusion

The multicomponent synthesis of a novel potentially bioactive series of dihydropyrimidin-2(1H)-ones/thione/imine based on 4-hydroxy-2-pyridone alkaloids has been provided by a rapid, straight, and efficient method using $ZnCl_2.2H_2O$ as inexpensive catalyst. The advantages of this reaction consist generality and simplicity operational, short reaction time, simple workup, and high to excellent yields and eco-compatibility.

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Declarations

Competing interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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