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PAPER

Thiamine hydrochloride (VB_1): an efficient promoter for the one-pot synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine and [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives in water medium†

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A straightforward and general method has been developed for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine and [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives by simply combining 2-aminobenzimidazole or 3-amino-1,2,4-triazole, aldehyde, and β-dicarbonyl compound in the presence of a catalytic amount of thiamine hydrochloride (VB_1). The advantages of this method are the use of an inexpensive and readily available catalyst, easy workup, improved yields, and the use of water as the solvent that is considered to be relatively environmentally benign.

Introduction

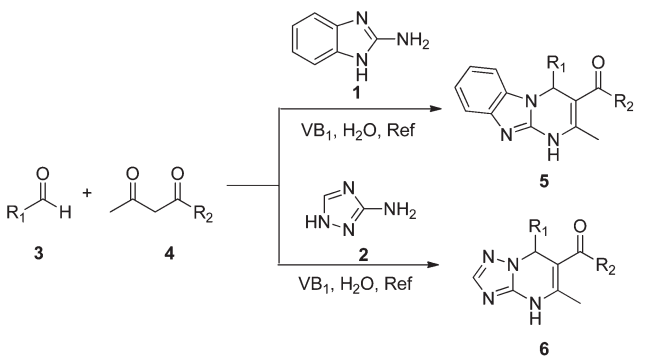
At the beginning of the new century, it is widely accredited that the development of efficient, practical and environmentally friendly methods of synthesis has been recognized as one of the most important topics of modern organic synthesis.[1] As the biggest pollution problem in many synthetic organic processes is with organic solvents, the development of efficient synthetic methodologies for organic reactions in the presence of non-toxic solvents is an important challenge.[2] It is known that water is a non-flammable, non-hazardous, non-toxic, uniquely redox-stable, inexpensive green solvent, therefore, using water as the reaction medium has gained considerable interest.[3] Moreover, the application of various metal ion free, environmentally safe, and convenient reagents in organic reactions has also received wide attention both in theory and practice.

In recent years, much attention has been devoted towards dihydropyrimidine derivatives due to their significant therapeutic and biological activities, such as TIE-2 and/or VEGFR2 inhibitory activities,[4] protein kinase inhibitor,[5] T cell activation,[6] antineoplastic activity,[7] lymphocyte specific kinase[8] and DNA-topoisomerase I.[9] Due to the importance of this heterocyclic compounds, various synthetic strategies have been developed which include: (i) NaOAc-catalyzed condensation of 2-aminobenzimidazole with arylmethyleneacetoacetate;[10] (ii) a three-component condensation reaction of aromatic aldehyde, β-dicarbonyl compound and 2-aminobenzimidazole catalyzed by an ionic liquid (*N*,*N*,*N*′,*N*′-tetramethylguanidinium trifluoroacetate[11] or [bmim]BF_4[12]), *N*,*N*′-dichlorobis(2,4,6-trichlorophenyl)urea,[13] H_2NSO_3H,[14] α-$Zr(CH_3)_{1.2}(O_3PC_6H_4SO_3H)_{0.8}$,[15] and microwave heating.[16]

Although, a number of modified methods under improved conditions have been reported, many of them suffer from one or more drawbacks, such as unsatisfactory yields, high temperature, long reaction times, and the use of toxic organic solvents and catalysts. Thus, it is necessary to further develop an efficient and convenient method to construct this type of heterocyclic compounds (Scheme 1).

It is well known that thiamine hydrochloride (VB_1) is a non-flammable, inexpensive, and non-toxic reagent which containing a pyrimidine ring and a thiazole ring linked by a methylene bridge (Fig. 1). VB_1 analogs as powerful catalysts have been applied in various organic transformations.[17] Recently, we have reported several VB_1-catalyzed reactions for the synthesis of heterocyclic compounds, such as pyrimidinones,[18] dihydropyridines,[19] and 1,2-dihydro-naphth[1,2-*e*][1,3]oxazine-3-one.[20]

As our ongoing efforts in exploring environmentally benign synthesis, herein we report an efficient and green procedure for



Scheme 1 Synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines **5** and [1,2,4]triazolo[1,5-*a*]pyrimidines **6**.

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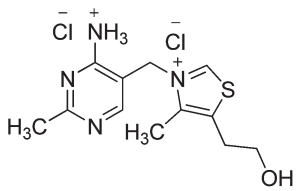
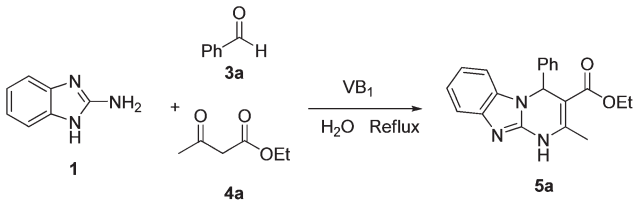


Fig. 1 The structure of thiamine hydrochloride (VB_1).

Table 1 Condensation of 2-aminobenzimidazole **1**, benzaldehyde **3a**, and ethyl acetoacetate **4a** in the presence of VB_1[a]



Entry	Catalyst (mol%)	Time (h)	Yield of **5a**[b] (%)
1	0	6	20
2	3	3	75
3[c]	5	3	90, 88, 85
4	10	3	90

[a] Conditions: 2-aminobenzimidazole **1** (2 mmol), benzaldehyde **3a** (2 mmol), and ethyl acetoacetate **4a** (2 mmol), H_2O (2 mL), reflux. [b] Isolated yields. [c] Catalyst was reused three times.

the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidine and [1,2,4]triazolo[1,5-*a*]pyrimidine derivatives in the presence of VB_1 in water.

Results and discussion

Optimization of the reaction conditions

Initially, we studied the three-component condensation reaction of 2-aminobenzimidazole **1a** (2 mmol) with benzaldehyde **3a** (2 mmol), and ethyl acetoacetate **4a** (2 mmol) in the presence of 3 mol% VB_1 in 2 mL H_2O at reflux temperature for 3 h to give the desired products **5a** in 75% yield. However, only 20% yield of the target product **5a** was observed when the mixture was stirred under similar conditions in the absence of VB_1 even after 6 h (Table 1, entry 1). Encouraged by the result, we further investigated the best reaction conditions by using different amounts of VB_1. An increase in the quantity of VB_1 from 0 mol % to 5 mol% not only decreased the reaction time from 6 h to 3 h, but also increased the product yield from 20% to 90% (Table 1, entries 1–3). However, the yield did not increased when excess amount (10 mol%) of VB_1 was used in this condensation reaction under the same conditions. Therefore, 5 mol% VB_1 was sufficient to catalyze this reaction.

The activity of the recycled VB_1 was also examined according to the typical experiment conditions. After the reaction was completed as indicated by TLC, the desired product **5a** was isolated by simple filtration. Then the filtered solution containing the catalyst was further treated with the reactants and the product **5a** was obtained in 90, 88, 85% yield after 1–3 runs, respectively (Table 1, entry 3). This study demonstrated that VB_1 could be effectively used as a reusable catalyst for this multi-component condensation.

Table 2 Condensation of 2-aminobenzimidazole **1**, benzaldehyde **3a**, and ethyl acetoacetate **4a** in different solvents[a]

Entry	Solvent	Temp. (°C)	Time (h)	Yield of **5a**[b] (%)
1	THF	Reflux	6	30
2	Toluene	100	6	50
3	MeCN	Reflux	6	60
4	DCM	Reflux	6	30
5	DMF	100	6	45
6	EtOH	Reflux	3	85
7	H_2O	Reflux	3	90
8	H_2O	40	10	20
9	H_2O	60	8	50
10	H_2O	80	6	65

[a] Conditions: 2-aminobenzimidazole **1** (2 mmol), benzaldehyde **3a** (2 mmol), and ethyl acetoacetate **4a** (2 mmol), VB_1 (0.1 mmol, 5 mol %), solvent (2 mL). [b] Isolated yields.

Then, the model reaction of 2-aminobenzimidazole **1a**, benzaldehyde **3a**, and ethyl acetoacetate **4a** catalyzed by VB_1 was chosen for investigating the effect of solvent and temperature (Table 2).

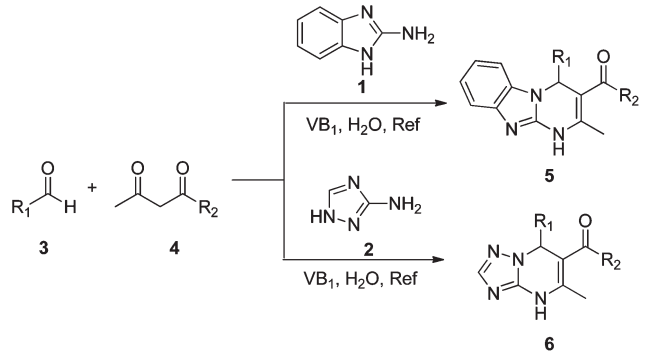
As shown in Table 2, low yields of the target product **5a** (30–50%) was obtained when the mixture was refluxed or 100 °C for 6 h in the presence of 5 mol% VB_1 in THF, DCM, toluene, and DMF (Table 2, entries 1, 2, 4, 5). The reaction using EtOH (85%) and H_2O (90%) as the solvents gave the corresponding product **5a** in high yields and short reaction time (Table 2, entries 6, 7). From the economical and environmental point of view, H_2O was chosen as the reaction medium for all further reactions. Furthermore, to optimize the temperature for the reaction, we carried out the reaction at temperatures ranging from 40 °C to reflux temperature using water as the reaction medium (Table 2, entries 7–10), finding that the yield of product was improved as the temperature was increased. Therefore, the best reaction conditions were obtained by using 5 mol% of VB_1 as the catalyst in H_2O at reflux temperature.

The scope of the substrates

To examine the extent of the catalyst's application in this condensation reaction, we applied the optimized reaction conditions to a series of aldehydes and two β-dicarbonyl compounds in the presence of 5 mol% VB_1 in H_2O at reflux temperature (Table 3).

In all of the studied examples, the aromatic, hetero-aromatic, and aliphatic aldehydes could react smoothly to give the corresponding benzo[4,5]imidazo[1,2-*a*]pyrimidines in good yields (Table 3, entries 1–19). Most importantly, aromatic aldehydes carrying either electron-donating or electron-withdrawing substituents including hydroxyl groups could react efficiently to give the corresponding products without significant difference. The catalyst exhibited remarkable activity where a variety of functional groups, such as OCH_3, CH_3, OH, CN, and Cl were well-tolerated, furnishing good yield of expected products. Moreover, we also used acetylacetone as the substrate, finding that the

Table 3 Synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines **5** and [1,2,4]triazolo[1,5-*a*]pyrimidines **6** catalyzed by VB_1[a]



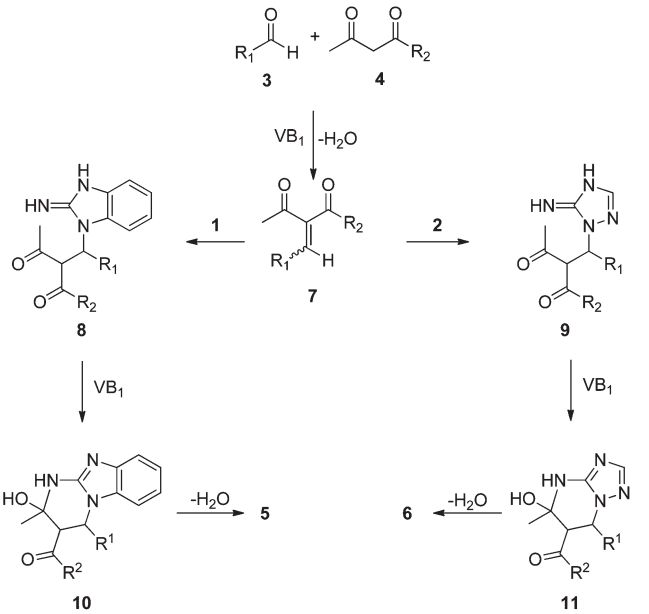
Entry	**1** or **2**	R^1	R_2	Product	Time (h)	Yield[b] (%)
1	**1**	C_6H_5	OEt	**5a**	3	90
2	**1**	4-ClC_6H_4	OEt	**5b**	3	90
3	**1**	3-ClC_6H_4	OEt	**5c**	3	91
4	**1**	2-ClC_6H_4	OEt	**5d**	3	90
5	**1**	4-$CH_3OC_6H_4$	OEt	**5e**	3	85
6	**1**	3,4-$(CH_3O)_2C_6H_3$	OEt	**5f**	3	91
7	**1**	4-HOC_6H_4	OEt	**5g**	4	87
8	**1**	4-$CH_3C_6H_4$	OEt	**5h**	4	88
9	**1**	4-OH-3-$CH_3OC_6H_3$	OEt	**5i**	4	88
10	**1**	4-NCC_6H_4	OEt	**5j**	3	91
11	**1**	4-Pyridyl	OEt	**5k**	3	93
12	**1**	2-Furyl	OEt	**5l**	4	85
13	**1**	CH_3CH_2	OEt	**5m**	3	96
14	**1**	$CH_3CH_2CH_2$	OEt	**5n**	3	95
15	**1**	$(CH_3)_2CH$	OEt	**5o**	4	92
16	**1**	C_6H_5	Me	**5p**	3	90
17	**1**	4-ClC_6H_4	Me	**5q**	3	93
18	**1**	4-$CH_3OC_6H_4$	Me	**5r**	3	86
19	**1**	3,4-$(CH_3O)_2C_6H_3$	Me	**5s**	3	90
20	**2**	C_6H_5	OEt	**6a**	6	80
21	**2**	4-ClC_6H_4	OEt	**6b**	6	83
22	**2**	4-$CH_3OC_6H_4$	OEt	**6c**	6	81
23	**2**	3,4-$(CH_3O)_2C_6H_3$	OEt	**6d**	6	81

[a] Conditions: aminobenzimidazole **1** or 3-amino-1,2,4-triazole **2** (2 mmol), aldehyde **3** (2 mmol), and ethyl acetoacetate **4a** or acetylacetone **4b** (2 mmol), VB_1 (0.1 mmol, 5 mol%), H_2O (2 mL), reflux. [b] Isolated yields.

reaction could proceed smoothly to give the corresponding products in excellent yields (86–93%) (Table 3, entries 16–19).

Furthermore, it is worth noting that [1,2,4]triazolo[1,5-*a*]pyrimidines are important building blocks in medicinal chemistry and have revealed diverse and interesting biological activities.[21] As for their preparation, the general methods are through a two-step strategy.[22] However, the reported methods were usually carried out in volatile organic solvents and required stoichiometric or excess corrosive acids, such as HCl,[23] AcOH,[24] and H_2NSO_3H,[25] which prompted us to study the possibility of extending the synthetic procedure developed above to the preparation of [1,2,4]triazolo[1,5-*a*]pyrimidines **6**.

Then, 3-amino-1,2,4-triazole **2** was employed under similar conditions to synthesise the corresponding products [1,2,4]triazolo[1,5-*a*]pyrimidines **6**. To our delight, 3-amino-1,2,4-triazole **2** was also a suitable substrate for this reaction and afforded the desired product **6** in excellent yields (Table 3, entries 20–23), albeit after a relatively long reaction time (6 h). The yields of the products were somewhat lower when using 3-amino-1,2,4-triazole (80–83%) as a substrate than using 2-aminobenzimidazole (85–91%).



Scheme 2 The probable mechanism of the VB_1-catalyzed condensation.

Probable mechanism for the condensation

We propose a mechanism of the VB_1-catalyzed condensation as shown in Scheme 2. First, we carried out the condensation of benzaldehyde **3a** and ethyl acetoacetate **4a** in the presence of 5 mol% VB_1 for 1 h, and the product ethyl 2-benzylidene-3-oxobutanoate **7a** was obtained in 10% yield. However, only a trace amount of the desired product **7a** was observed when the condensation was carried out in the absence of VB_1. This result revealed that VB_1 could promote Knoevenagel condensation of benzaldehyde **3a** and ethyl acetoacetate **4a**. Then, we mixed ethyl 2-benzylidene-3-oxobutanoate **7a** and aminobenzimidazole **1** in water under reflux temperature for 3 h, finding the reaction was sluggish and only 30% yield of the corresponding product **5a** was obtained. Hence, we think that the condensation of 2-aminobenzimidazole **1** or 3-amino-1,2,4-triazole **2**, aldehyde **3** and β-dicarbonyl compound **4** may occur by the mechanism of Knoevenagel condensation, Michael addition, cyclization, and dehydration. Initially, this reaction may proceed *via* intermediate **7**, formed by the Knoevenagel condensation of aldehyde **3** and β-dicarbonyl compound **4** under the action of VB_1. Then, Michael addition between **7** and **1** or **2** leads to the formation of intermediate **8** or **9** at the action of VB_1, followed by cyclization and dehydration, affords the corresponding products **5** or **6**.

Conclusions

In summary, we have developed an efficient and convenient method for the synthesis of benzo[4,5]imidazo[1,2-*a*]

pyrimidines and [1,2,4]triazolo[1,5-*a*]pyrimidines *via* the three-component condensation reactions of 2-aminobenzimidazole **1** or 3-amino-1,2,4-triazole **2**, aldehyde **3** and β-dicarbonyl compound **4** catalyzed by VB_1 in water. The operational simplicity, mild reaction conditions, short reaction time, and minimal environmental impact are notable features of this procedure. Hence, it is a useful addition to the existing methods.

Experimental

Melting points were measured by a WRS-1B micromelting point apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX 300 instrument or Bruker AMX 400 instrument using solvent peaks as DMSO-d_6 solutions. HRESIMS were determined on a Micromass Q-Tif Global mass spectrometer and ESIMS were run on a Bruker Esquire 3000 Plus Spectrometer. TLC was performed on GF254 silica gel plates (Yantai Huiyou Inc., China).

General procedure for the synthesis of benzo[4,5]imidazo[1,2-*a*]pyrimidines 5 or [1,2,4]triazolo[1,5-*a*]pyrimidines 6

A mixture of 2-aminobenzimidazole **1** or 3-amino-1,2,4-triazole **2** (2 mmol), aldehyde **3** (2 mmol), β-dicarbonyl compound **4** (2 mmol), and VB_1 (0.1 mmol, 5 mol%) in water (2 mL) was heated to reflux for 3–6 h. After completion of the reaction (TLC), the solid was filtered off, washed with water and recrystallized from ethanol (5 mL) to yield pure product **5** or **6**.

Ethyl 2-methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5a)

White powder, m.p. 287.5–287.7 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.81 (brs, 1H, NH), 7.34 (m, 3H, ArH), 7.25 (m, 3H, ArH), 7.16 (t, J = 7.2 Hz, 1H, ArH), 7.02 (t, J = 7.6 Hz, 1H, ArH), 6.93 (t, J = 7.5 Hz, 1H, ArH), 6.41 (s, 1H, CH), 4.00 (q, J = 7.1 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.13 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.1, 146.5, 145.5, 142.2, 142.0, 131.5, 128.3, 128.3, 127.7, 127.1, 127.1, 121.7, 120.1, 116.7, 109.8, 97.9, 59.3, 55.9, 18.6, 14.0; ESI-MS m/z 334 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{20}N_3O_2$ $[M + H]^+$ 334.1556, found 334.1552.

Ethyl 4-(4-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5b)

Yellowish powder; m.p. 291.4–292.2 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.86 (brs, 1H, NH), 7.39–7.27 (m, 5H, ArH), 7.23 (d, J = 7.4 Hz, 1H, ArH), 7.02 (td, J = 7.7, 1.2 Hz, 1H, ArH), 6.93 (td, J = 7.6, 1.1 Hz, 1H), 6.43 (s, 1H, CH), 3.99 (q, J = 7.1 Hz, 2H, CH_2), 2.43 (s, 3H, CH_3), 1.12 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.0, 146.8, 145.4, 142.3, 141.0, 132.3, 131.4, 129.0, 129.0, 128.4, 128.4, 121.9, 120.2, 116.8, 109.8, 97.4, 59.4, 55.2, 18.7, 14.1; ESI-MS m/z 368 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{19}ClN_3O_2$ $[M + H]^+$ 368.1166, found 368.1168.

Ethyl 4-(3-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5c)

Yellowish powder; m.p. 269.6–269.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.91 (brs, 1H, NH), 7.44 (s, 1H, ArH), 7.34 (d, J = 7.8 Hz, 1H, ArH), 7.26 (m, 4H, ArH), 7.03 (t, J = 7.5 Hz, 1H, ArH), 6.94 (t, J = 7.5 Hz, 1H, ArH), 6.44 (s, 1H, CH), 4.01 (q, J = 7.1 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.12 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (10 MHz, DMSO-d_6) δ_C: 165.0, 147.1, 145.4, 144.4, 142.2, 132.8, 131.4, 130.4, 127.8, 127.1, 125.7, 121.9, 120.4, 116.9, 109.9, 97.3, 59.5, 55.3, 18.7, 14.0; ESI-MS m/z 368 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{19}ClN_3O_2$ $[M + H]^+$ 368.1166, found 368.1169.

Ethyl 4-(2-chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5d)

Yellowish powder; m.p. 291.3–292.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.93 (brs, 1H, NH), 7.45–7.29 (m, 3H, ArH), 7.27–7.14 (m, 3H, ArH), 7.01 (t, J = 4.2 Hz, 1H, ArH), 6.92 (t, J = 7.6 Hz, 1H, ArH), 6.71 (s, 1H, CH), 3.96 (q, J = 7.1 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.05 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.5, 147.8, 145.7, 142.6, 139.3, 132.2, 132.1, 131.0, 130.1, 129.9, 128.3, 122.4, 120.8, 117.4, 109.7, 96.8, 59.7, 54.2, 19.1, 14.5. ESI-MS m/z 368 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{19}ClN_3O_2$ $[M + H]^+$ 368.1166, found 368.1163.

Ethyl 4-(4-methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5e)

White powder; m.p. 272.3–273.0 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.73 (brs, 1H, NH), 7.31 (d, J = 7.5 Hz, 1H, ArH), 7.28–7.19 (m, 3H, ArH), 7.00 (dd, J = 8.4, 3.8 Hz, 1H, ArH), 6.92 (dd, J = 8.3, 3.8 Hz, 1H, ArH), 6.78 (d, J = 8.7 Hz, 2H, ArH), 6.35 (s, 1H, CH), 3.99 (q, J = 7.1 Hz, 2H, CH_2), 3.63 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 1.13 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.2, 158.6, 146.2, 145.6, 142.3, 134.2, 131.5, 128.3, 128.3, 121.7, 120.1, 116.7, 113.7, 113.7, 109.9, 98.2, 59.4, 55.3, 54.9, 18.6, 14.1; ESI-MS m/z 364 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{22}N_3O_3$ $[M + H]^+$ 364.1661, found 364.1664.

Ethyl 4-(3,4-dimethoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5f)

Yellowish powder; m.p. 261.3–261.9 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.43 (brs, 1H, NH), 6.94 (d, J = 7.7 Hz, 1H, ArH), 6.87 (d, J = 7.5 Hz, 1H, ArH), 6.72–6.43 (m, 5H, ArH), 6.17 (s, 1H, CH), 3.64 (q, J = 6.8 Hz, 2H, CH_2), 3.33 (s, 3H, CH_3), 3.29 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 0.74 (t, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.4, 152.3, 146.7, 146.3, 145.7, 142.1, 133.8, 131.8, 123.4, 121.5, 121.5, 119.9, 116.6, 112.5, 109.6, 96.5, 59.9, 59.2, 55.5, 52.6, 18.9, 14.2; ESI-MS m/z 394 $[M + H]^+$; HRMS (ESI) calcd for $C_{22}H_{24}N_3O_4$ $[M + H]^+$ 394.1767, found 394.1763.

Ethyl 4-(4-hydroxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5g)

White solid; m.p. 261.6–261.7 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.72 (brs, 1H, NH), 9.36 (brs, 1H, OH), 7.31 (d, J = 7.8 Hz, 1H, ArH), 7.21 (d, J = 7.8 Hz, 1H, ArH), 7.13 (d, J = 8.2 Hz, 2H, ArH), 7.00 (t, J = 7.5 Hz, 1H, ArH), 6.92 (t, J = 7.4 Hz, 1H, ArH), 6.60 (d, J = 8.2 Hz, 2H, ArH), 6.29 (s, 1H, CH), 3.98 (q, J = 7.0 Hz, 2H, CH_2), 2.42 (s, 3H, CH_3), 1.12 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.3, 156.8, 145.9, 145.6, 142.3, 132.5, 131.6, 128.3, 128.3, 121.6, 120.0, 116.7, 114.9, 114.9, 109.9, 98.3, 59.3, 55.5, 18.6, 14.1; ESI-MS m/z 350 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{20}N_3O_3$ $[M + H]^+$ 350.1505, found 350.1509.

Ethyl 2-methyl-4-(*p*-tolyl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5h)

Yellowish powder; m.p. 262.2–262.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.81 (brs, 1H, NH), 7.32 (d, J = 7.8 Hz, 1H, ArH), 7.20 (d, J = 7.9 Hz, 3H, ArH), 7.07–6.97 (m, 3H, ArH), 6.91 (t, J = 7.2 Hz, 1H, ArH), 6.35 (s, 1H, CH), 3.98 (q, J = 7.1 Hz, 2H, CH_2), 2.43 (s, 3H, CH_3), 2.15 (s, 3H, CH_3), 1.12 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.2, 146.3, 145.6, 142.3, 139.1, 136.9, 131.5, 128.9, 128.9, 126.9, 126.9, 121.7, 120.1, 116.7, 109.9, 97.9, 59.3, 55.6, 20.6, 18.6, 14.1; ESI-MS m/z 348 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{22}N_3O_2$ $[M + H]^+$ 348.1712, found 348.1710.

Ethyl 4-(4-hydroxy-3-methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5i)

White solid; m.p. > 270 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.70 (brs, 1H, NH), 8.94 (brs, 1H, OH), 7.30 (dd, J = 7.5, 3.6 Hz, 2H, ArH), 6.97 (m, 3H, ArH), 6.68–6.55 (m, 2H, ArH), 6.30 (s, 1H, CH), 4.00 (q, J = 7.1 Hz, 2H, CH_2), 3.70 (s, 3H, CH_3), 2.42 (s, 3H, CH_3), 1.14 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.3, 146.9, 146.1, 145.9, 145.7, 142.3, 133.2, 131.6, 121.7, 120.0, 119.3, 116.7, 115.4, 111.9, 110.1, 98.3, 59.3, 55.7, 55.63, 18.6, 14.2; ESI-MS m/z 380 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{22}N_3O_4$ $[M + H]^+$ 380.1610, found 380.1614.

Ethyl 4-(4-cyanophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5j)

Yellowish powder; m.p. > 275 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.96 (brs, 1H, NH), 7.72 (d, J = 8.0 Hz, 2H, ArH), 7.54 (d, J = 8.1 Hz, 2H, ArH), 7.33 (d, J = 7.7 Hz, 1H, ArH), 7.24 (d, J = 7.8 Hz, 1H, ArH), 7.02 (t, J = 7.4 Hz, 1H, ArH), 6.93 (t, J = 7.5 Hz, 1H, ArH), 6.51 (s, 1H, CH), 3.98(q, J = 7.0 Hz, 2H), 2.46 (s, 3H, CH_3), 1.11 (t, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 164.9, 147.4, 147.1, 145.3, 142.2, 132.5, 132.5, 131.3, 128.2, 128.2, 122.0, 120.4, 118.5, 116.9, 110.6, 109.8, 96.9, 59.5, 55.5, 18.7, 14.0; ESI-MS m/z 359 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{19}N_4O_2$ $[M + H]^+$ 359.1508, found 359.1505.

Ethyl 2-methyl-4-(pyridin-4-yl)-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5k)

White solid; m.p. > 250 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.95 (brs, 1H, NH), 8.45 (d, J = 5.6 Hz, 2H, ArH), 7.33 (m, 3H, ArH), 7.25 (d, J = 7.7 Hz, 1H, ArH), 7.03 (t, J = 7.6 Hz, 1H, ArH), 6.94 (t, J = 7.6 Hz, 1H, ArH), 6.44 (s, 1H, CH), 4.01 (q, J = 7.1 Hz, 2H, CH_2), 2.45 (s, 3H, CH_3), 1.12 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 164.9, 150.0, 150.0, 149.9, 147.6, 145.4, 142.2, 131.4, 122.1, 122.1, 122.0, 120.4, 116.9, 109.8, 96.5, 59.5, 54.9, 18.7, 14.1; ESI-MS m/z 335 $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{19}N_4O_2$ $[M + H]^+$ 335.1508, found 335.1506.

Ethyl 4-(furan-2-yl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5l)

Yellowish solid; m.p. > 245 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.84 (brs, 1H, NH), 7.42 (s, 1H, ArH), 7.40 (d, J = 6.0 Hz,, 1H, ArH), 7.34 (d, J = 7.9 Hz, 1H, ArH), 7.12–6.96 (m, 2H, ArH), 6.54 (s, 1H, ArH), 6.43 (d, J = 3.1 Hz, 1H, ArH), 6.29 (dd, J = 3.1, 1.8 Hz, 1H, CH), 4.04 (q, J = 7.1 Hz, 2H, CH_2), 2.44 (s, 3H, CH_3), 1.13 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.1, 152.7, 147.8, 145.6, 142.6, 142.2, 131.5, 121.9, 120.3, 116.8, 110.4, 109.8, 107.7, 94.3, 59.3, 49.1, 18.7, 14.1; ESI-MS m/z 324 $[M + H]^+$; HRMS (ESI) calcd for $C_{18}H_{18}N_3O_3$ $[M + H]^+$ 324.1348, found 324.1344.

Ethyl 4-ethyl-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5m)

White solid; m.p. 192.5–192.9 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.49 (brs, 1H, NH), 7.50–7.28 (m, 2H, ArH), 7.06 (m, 2H, ArH), 5.58 (t, J = 3.6 Hz, 1H, CH), 4.14 (q, J = 7.1 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.08–1.90 (m, 1H, CH_2), 1.66 (m, 1H, CH_2), 1.23 (t, J = 7.1 Hz, 3H, CH_3), 0.48 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.5, 148.2, 146.9, 142.3, 131.4, 121.6, 120.2, 116.9, 109.4, 94.9, 59.3, 52.3, 26.4, 18.7, 14.3, 7.1; ESI-MS m/z 286 $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{20}N_3O_2$ $[M + H]^+$ 286.1556, found 286.1558.

Ethyl 2-methyl-4-propyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5n)

White solid; m.p. 191.2–191.3 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.53 (brs, 1H, NH), 7.38 (m, 2H, ArH), 7.05 (m, 2H, ArH), 5.55 (t, J = 3.6 Hz, 1H, CH), 4.14 (q, J = 6.3 Hz, 2H, CH_2), 2.36 (s, 3H, CH_3), 1.96–1.80 (m, 1H, CH_2), 1.61 (m, 1H, CH_2), 1.23 (t, J = 6.3 Hz, 3H, CH_3), 1.17 (m, 1H, CH_2), 0.68 (m, 4H, CH_2CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.5, 147.9, 146.8, 142.3, 131.5, 121.6, 120.2, 116.8, 109.32, 95.8, 59.4, 51.6, 36.2, 18.7, 16.2, 14.3, 13.7; ESI-MS m/z 300 $[M + H]^+$; HRMS (ESI) calcd for $C_{17}H_{22}N_3O_2$ $[M + H]^+$ 300.1712, found 300.1715.

Ethyl 4-isopropyl-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidine-3-carboxylate (5o)

White solid; m.p. 197.5–197.9 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.49 (brs, 1H, NH), 7.58–7.22 (m, 2H, ArH), 7.14–6.88 (m, 2H, ArH), 5.47 (d, J = 2.9 Hz, 1H, CH), 4.13 (q, J = 7.1 Hz, 2H, CH_2), 2.37 (s, 3H, CH_3), 2.20–2.02 (m, 1H, CH), 1.24 (t, J = 7.1 Hz, 3H, CH_3), 0.73 (dd, J = 6.9 Hz, 3H, CH_3), 0.66 (dd, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.9, 148.0, 147.5, 142.3, 131.9, 121.5, 119.9, 116.75, 109.9, 95.0, 59.4, 56.2, 35.6, 19.2, 18.5, 17.1, 14.2; ESI-MS m/z 300 $[M + H]^+$; HRMS (ESI) calcd for $C_{17}H_{22}N_3O_2$ $[M + H]^+$ 300.1712, found 300.1716.

1-(2-Methyl-4-phenyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-3-yl)ethanone (5p)

Yellowish powder; m.p. > 275 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.79 (brs, 1H, NH), 7.39 (d, J = 7.0 Hz, 3H, ArH), 7.32 (d, J = 7.6 Hz, 1H, ArH), 7.24 (t, J = 7.3 Hz, 2H, ArH), 7.15 (m, 1H, ArH), 6.98 (m, 2H, ArH), 6.57 (s, 1H, CH), 2.46 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.6, 146.7, 145.9, 142.8, 142.2, 132.1, 129.0, 129.0, 128.3, 127.7, 127.7, 122.2, 120.6, 117.3, 110.5, 109.2, 56.1, 31.2, 20.2; ESI-MS m/z 304 $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{18}N_3O$ $[M + H]^+$ 304.1450, found 304.1452.

1-(4-(4-Chlorophenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-3-yl)ethanone (5q)

Yellowish powder; m.p. > 285 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.85 (brs, 1H, NH), 7.35 (m, 6H, ArH), 6.99 (m, 2H, ArH), 6.57 (s, 1H, CH), 2.46 (s, 3H, CH_3), 2.22 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 193.9, 146.5, 145.4, 142.3, 140.7, 132.4, 131.5, 129.02, 129.0, 128.5, 128.5, 121.9, 120.3, 116.9, 109.9, 108.6, 54.9, 30.8, 19.8; ESI-MS m/z 338 $[M + H]^+$; HRMS (ESI) calcd for $C_{19}H_{17}ClN_3O$ $[M + H]^+$ 338.1060, found 338.1063.

1-(4-(4-Methoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-3-yl)ethanone (5r)

White powder; m.p. 278.6–279.5 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.74 (br s, 1H, NH), 7.40 (d, J = 7.0 Hz, 1H, ArH), 7.37–7.23 (m, 3H, ArH), 6.99 (m, 2H, ArH), 6.79 (d, J = 8.6 Hz, 2H, ArH), 6.54 (s, 1H, CH), 3.63 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.18 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.3, 158.7, 145.8, 145.5, 142.3, 133.7, 131.6, 128.5, 128.5, 121.7, 120.1, 116.8, 113.8, 113.8, 110.1, 108.7, 55.1, 54.9, 30.6, 19.7; ESI-MS m/z 334 $[M + H]^+$; HRMS (ESI) calcd for $C_{20}H_{20}N_3O_2$ $[M + H]^+$ 334.1556, found 334.1553.

1-(4-(3,4-Dimethoxyphenyl)-2-methyl-1,4-dihydrobenzo[4,5]imidazo[1,2-*a*]pyrimidin-3-yl)ethanone (5s)

Yellowish powder; m.p. 268.7–269.3 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.73 (brs, 1H, NH), 7.48 (d, J = 7.2 Hz, 1H, ArH), 7.31 (d, J = 7.5 Hz, 1H, ArH), 7.16–6.93 (m, 3H, ArH), 6.82 (m, 2H, ArH), 6.53 (s, 1H, CH), 3.68 (s, 3H, CH_3), 3.62 (s, 3H, CH_3), 2.45 (s, 3H, CH_3), 2.20 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 194.9, 148.8, 148.8, 146.3, 145.9, 142.8, 134.6, 132.1, 122.17, 120.6, 119.8, 117.3, 112.3, 111.8, 110.7, 109.0, 56.0, 55.9, 55.8, 31.0, 20.1; ESI-MS m/z 364 $[M + H]^+$; HRMS (ESI) calcd for $C_{21}H_{22}N_3O_3$ $[M + H]^+$ 364.1661, found 364.1660.

Ethyl 5-methyl-7-phenyl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (6a)

White solid; m.p. 205.6–206.4 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.79 (brs, 1H, NH), 7.62 (s, 1H, ArH), 7.32–7.14 (m, 5H, ArH), 6.24 (s, 1H, CH), 3.98 (q, J = 7.1 Hz, 2H), 2.39 (s, 3H, CH_3), 1.01 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.1, 150.1, 146.9, 146.7, 142.1, 128.3, 128.3, 127.9, 126.9, 126.9, 97.2, 59.5, 59.3, 18.4, 13.9; ESI-MS m/z 285 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{17}N_4O_2$ $[M + H]^+$ 285.1352, found 285.1354.

Ethyl 7-(4-chlorophenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (6b)

White solid; m.p. 258.7–258.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.84 (brs, 1H, NH), 7.64 (s, 1H, ArH), 7.34 (d, J = 8.5 Hz, 2H, ArH), 7.22 (d, J = 8.5 Hz, 2H, ArH), 6.26 (s, 1H, CH), 3.96 (q, J = 7.1 Hz, 2H, CH_2), 2.39 (s, 3H, CH_3), 1.01 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 164.9, 150.3, 147.1, 146.9, 141.1, 132.5, 128.9, 128.9, 128.37, 128.4, 96.7, 59.4, 58.9, 18.5, 13.9; ESI-MS m/z 319 $[M + H]^+$; HRMS (ESI) calcd for $C_{15}H_{16}ClN_4O_2$ $[M + H]^+$ 319.0962, found 319.0964.

Ethyl 7-(4-methoxyphenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (6c)

White solid; m.p. 237.5–237.9 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.73 (brs, 1H, NH), 7.61 (s, 1H, ArH), 7.11 (d, J = 8.6 Hz, 2H, ArH), 6.82 (d, J = 8.6 Hz, 2H, ArH), 6.20 (s, 1H, CH), 3.96 (q, J = 7.1 Hz, 2H, CH_2), 3.67 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 1.03 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.2, 158.8, 150.0, 146.9, 146.4, 134.3, 134.3, 128.2, 128.2, 113.7, 97.4, 59.3, 58.9, 55.0, 18.4, 13.9; ESI-MS m/z 315 $[M + H]^+$; HRMS (ESI) calcd for $C_{16}H_{19}N_4O_3$ $[M + H]^+$ 315.1457, found 315.1454.

Ethyl 7-(3,4-dimethoxyphenyl)-5-methyl-4,7-dihydro-[1,2,4]triazolo[1,5-*a*]pyrimidine-6-carboxylate (6d)

White solid; m.p. 192.5–192.8 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 10.72 (brs, 1H, NH), 7.62 (s, 1H, ArH), 6.82 (m, 2H, ArH), 6.64 (dd, J = 8.3, 1.9 Hz, 1H, ArH), 6.19 (s, 1H, CH), 3.96 (q, J = 7.1 Hz, 2H, CH_2), 3.68 (s, 3H, CH_3), 3.67 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 1.04 (t, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6) δ_C: 165.7, 150.5, 148.9, 148.7, 147.4, 146.8, 135.2, 119.4, 112.2, 111.6, 97.9, 59.8, 59.7, 55.9, 55.9, 18.9, 14.4; ESI-MS m/z 345 $[M + H]^+$; HRMS (ESI) calcd for $C_{17}H_{21}N_4O_4$ $[M + H]^+$ 345.1563, found 345.1560.

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