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Synthesis of fused pyridines in the presence of thiamine hydrochloride as an efficient and reusable catalyst in aqueous conditions

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Efficient and straightforward synthesis of fused pyridine derivatives was achieved from electron-rich amino heterocycles and Knoevenagel products derived from aldehyde and malononitrile under aqueous media at 90 °C in the presence of thiamine hydrochloride as a reusable, green catalyst. The strategy in this protocol involves addition on an activated olefinic bond formed *in situ* by Knoevenagel condensation between an aromatic aldehyde and an active methylene compound. The Michael product on subsequent cyclo condensation yielded fused pyridine in high yield. It offers several advantages such as inexpensive, easily available and recyclable catalyst, simple operational procedure, excellent yield and use of aqueous medium that is considered to be relatively eco-friendly. Vitamin B1 was recovered and reused thrice.

Introduction

Industrial and academic researchers during the last ten years have developed and recognized the one pot multicomponent reaction as an effective tool for combinatorial synthesis in drug discovery processes.[1–3] Multicomponent reactions (MCRs) have been proven to be a powerful and efficient tool with unique advantages of atom economy, low waste, quick assembly of molecules of complex structure and furnishing diverse molecules for optimization processes for drug discovery research.[4] It is a challenge in the field of modern chemical research to develop efficient and non-hazardous methods to perform organic synthesis. Most solvents used in organic synthesis have hazardous effects on the environment and human beings. In view of the above overwhelming challenges, water, being an ideal green solvent, is commonly used as a reaction medium and is gaining more and more importance in the field of modern organic synthesis.[5]

As part of recent investigations in the field of biocatalysis, thiamine hydrochloride (VB1) and its analogues have been used as versatile catalysts which has reflected their applications in diverse organic reactions and transformations, for example Knoevenagel condensation, Michael addition and cyclisation.[6–9] In creating carbon–carbon bonds and carbon–heteroatom bonds in various ongoing transformations, VB1 as a green catalyst has created enormous interest in researchers[10] because of its non-toxicity, low cost, ease of handling and water and air compatibility.[11] Many heterocycles containing pyrido[2,3-*d*]pyrimidines and naphthyridines as a core unit reflect the large spectrum of biological, therapeutic and pharmaceutical activities such as antifoliate,[12] antitumour,[13] antihypertensive,[14] cyclin-dependent kinase 4 inhibition,[15] anti-inflammatory,[16] and antibacterial,[17] which can be used in drug discovery. Naphthyridines are also used in the chemotherapy of infectious disease,[18] as a growth regulator,[19] inhibitor of HIV-1integrase *in vitro* and infected cell.[20] Substituted 2-aminopyridine-3-carbonitriles are also used as cholinergic and neuroprotective drugs for the treatment of Alzheimer's and neuronal vascular diseases.[21] A literature survey reveals different types of modified methods for the synthesis of pyrido[2,3-*d*]pyrimidine-6-carbonitrile and [1,8]-naphthyridine-3-carbonitrile under different and improved conditions using diammonium hydrogen phosphate, microwave,[22] bismuth(III)-nitrate pentahydrate,[23] magnesium oxide[24] and TEBAC.[25a,b] However, so far most of these methods suffer from one or more problems such as the use of toxic organic solvents, use of expensive metals as catalysts, harsh reaction conditions, volatile solvents, non-recyclability of catalysts and lower yield.[26–28]

Result and discussion

In this manuscript we investigated the synthesis of pyrido[2,3-*d*]-pyrimidine-6-carbonitrile, [1,8]-naphthyridine-3-carbonitrile and their derivatives by using VB1 as a catalyst in the presence of water for the first time. It is also known to all that this biocatalyst is a stable and storable reagent which contains a pyrimidine ring and a thiazole ring linked by a methylene bridge.[29] To the best of

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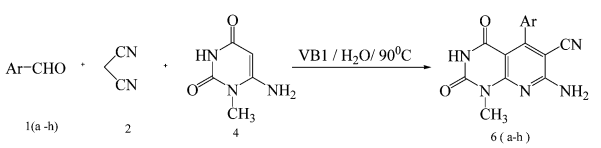
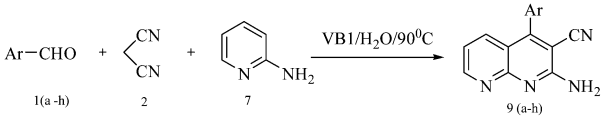
our knowledge there are no reports on the three-component one-pot synthesis of pyrido[2,3-*d*]pyrimidine-6-carbonitriles and [1,8]-naphthyridine-3-carbonitriles using thiamine hydrochloride as catalyst in the presence of water. In continuation of our work on the multicomponent synthesis of heterocyclic scaffolds by environmentally benign methods,[30] herein we report a highly efficient one-pot protocol for the synthesis of pyrido[2,3-*d*]pyrimidine-6-carbonitriles and [1,8]-naphthyridine-3-carbonitriles *via* the three component condensation of aldehydes, malononitrile and electron-rich amino heterocycles like 6-amino-1-methyluracil and 2-aminopyridine catalyzed by VB1 in water at 90 °C. At first, the reaction was performed in two steps. In the first step, benzylidene malononitrile **3** was obtained in 89% yield by the VB1-promoted Knoevenagel condensation of 4-methoxybenzaldehyde with malononitrile in water at 90 °C. In the second step, the isolated benzylidene malononitrile **3** was treated with 6-amino-1-methyluracil (Scheme 1) and 2-aminopyridine (Scheme 2) separately in the presence of VB1 under similar conditions to afford the desired products (**6** and **9**) with excellent yield. In order to make the synthesis more convenient, we preferred to perform the above two steps in a one-pot procedure.

In our initial endeavour to synthesize pyrido[2,3-*d*]pyrimidine-6-carbonitriles, the reaction of 6-amino-1-methyluracil, 4-methoxybenzaldehyde and malononitrile were carried out in the absence of any catalyst at 90 °C. The reaction did not occur even after 12 h. To investigate the suitable conditions, the model reaction was performed in the presence of various catalysts such as SiO_2, $ZnCl_2$, $MgCl_2$, Al_2O_3 and alum in the presence of water at 90 °C. The results summarized in Table 1 revealed that the reaction did not occur in the presence of SiO_2, Al_2O_3 or alum and in the presence of $MgCl_2$ and $ZnCl_2$ the yield was very low.

Then we conducted the above reaction in the presence of VB1 in water at 90 °C. It was observed that reactivity was much improved and the reaction was completed within 2.0–2.5 h, affording the solid product in excellent yield. Now we focused our attention to optimize the amount of catalyst. For this, a model reaction was carried out under different amounts of catalyst (Table 2). After some experiments, we observed that the use of 10 mol% VB1 instead of 5 mol% dramatically increased the yield of product (Table 2, entries 2 and 3). However the use of 15 mol% of catalyst showed the same yield and the same time was required for the synthesis of the products (Table 2, entry 4).



Scheme 1 VB1-catalyzed synthesis of pyrido[2,3-*d*]pyrimidine-6-carbonitriles.



Scheme 2 VB1-catalyzed synthesis of [1,8]-naphthyridine-3-carbonitriles.

Table 1 Influence of various catalysts on synthesis of compounds **6c** and **9c**

				Yield[c] (%)	
Entry	Solvent	Catalyst (10 mol%)	Time (h)	**6c**[a]	**9c**[b]
1	H_2O	—	12	—	—
2	H_2O	$ZnCl_2$	12	19	17
3	H_2O	$MgCl_2$	12	22	25
4	H_2O	SiO_2	12	—	—
5	H_2O	Al_2O_3	12	—	—
6	H_2O	Alum	12	—	—
7	H_2O	VB1	2.5	94	95

[a] Reaction conditions: 4-methoxybenzaldehyde (1 mmol), malononitrile (1 mmol) and 6-amino-1-methyluracil (1 mmol) were stirred in 4 mL water in the presence of catalyst (10 mol%) at 90 °C. [b] Reaction conditions: 4-methoxybenzaldehyde (1 mmol), malononitrile (1 mmol) and 2-amino pyridine (1 mmol) were stirred in 4 mL water in the presence of catalyst (10 mol%) at 90 °C. [c] Isolated yield of product.

Table 2 Optimization of mol% of catalyst for the synthesis of compounds **6c** and **9c**

			Yield[c] (%)	
Entry	Catalyst (mol%)	Time (h)	**6c**[a]	**9c**[b]
1	0	14	—	—
2	5	10	40	47
3[d]	10	2.5	94,91,91	95,93,89
4	15	2.5	94	95

[a] Reaction conditions: 4-methoxybenzaldehyde (1 mmol), malononitrile (1 mmol) and 6-amino-1-methyluracil (1 mmol) were stirred in 4 mL water in the presence of catalyst at 90 °C. [b] Reaction conditions: 4-methoxybenzaldehyde (1 mmol), malononitrile (1 mmol) and 2-amino pyridine (1 mmol) were stirred in 4 mL water in the presence of catalyst at 90 °C. [c] Isolated yield of product. [d] Catalyst was reused three times.

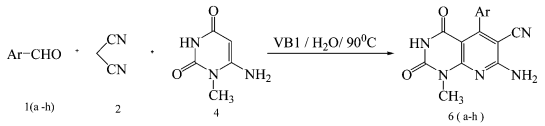
With the hope of increasing the yield, the reactions were performed in other solvents such as non-polar (DCM, toluene, dioxan), polar aprotic (CH_3CN, THF, DMF) and polar protic (H_2O, MeOH) (Table 3); however, water was found to be the best solvent for carrying out this VB1-promoted conversion.

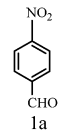
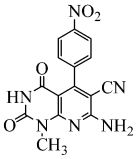
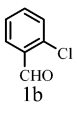
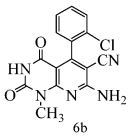
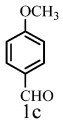
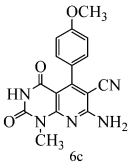
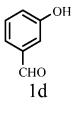
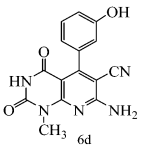
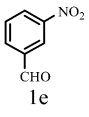
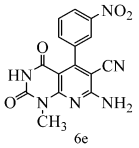
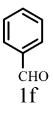
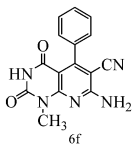
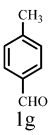
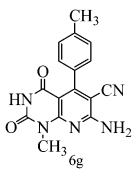
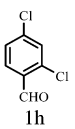
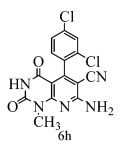
Table 3 Optimization of reaction conditions with respect to solvent and temperature for the synthesis of compounds **6c** and **9c**

				Yield[a] (%)	
Entry	Catalyst (10 mol%)	Solvent	Temp.	**6c**[b]	**9c**[c]
1	VB1	H_2O	90 °C	94	95
2	VB1	H_2O	50 °C	30	18
3	VB1	H_2O	r.t.	—	—
4	VB1	DCM	Reflux	63	59
5	VB1	THF	Reflux	45	47
6	VB1	CH_3CN	Reflux	61	55
7	VB1	Dioxan	Reflux	14	15
8	VB1	H_2O	90 °C	94	95
9	VB1	DMF	Reflux	29	25
10	VB1	MeOH	Reflux	54	51
11	VB1	Toluene	Reflux	23	19

[a] Isolated yield of product. [b] 4-Methoxybenzaldehyde (1 mmol), malononitrile (1 mmol) and 6-amino-1-methyluracil (1 mmol) were stirred in 4 mL water in the presence of catalyst (10 mol%) at 90 °C. [c] 4-Methoxybenzaldehyde (1 mmol), malononitrile (1 mmol) and 2-aminopyridine (1 mmol) were stirred in 4 mL water in the presence of catalyst (10 mol%) at 90 °C.

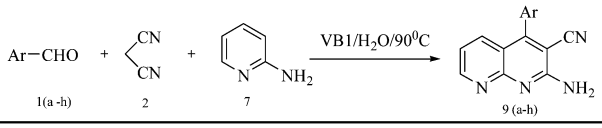
Table 4 Substrate scope for the formation of compound **6**

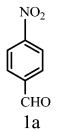
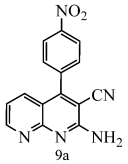
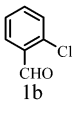
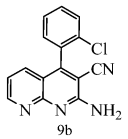
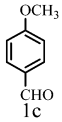
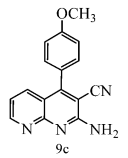
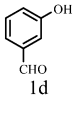
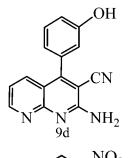
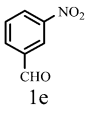
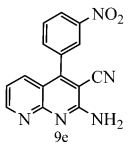
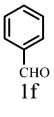
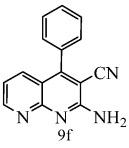
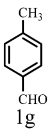
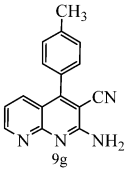
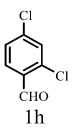
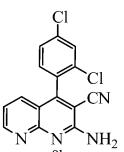


Entry	Aldehyde **1(a–h)**	Product **6(a–h)**[a]	Time (h)	Yield[b] (%)
1	 1a	 6a	2.5	94
2	 1b	 6b	2.5	94
3	 1c	 6c	2.0	92
4	 1d	 6d	2.5	93
5	 1e	 6e	2.0	93
6	 1f	 6f	2.0	93
7	 1g	 6g	2.5	94
8	 1h	 6h	2.5	94

[a] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. [b] Isolated yield of pure product.

Table 5 Substrate scope for formation of product **9**



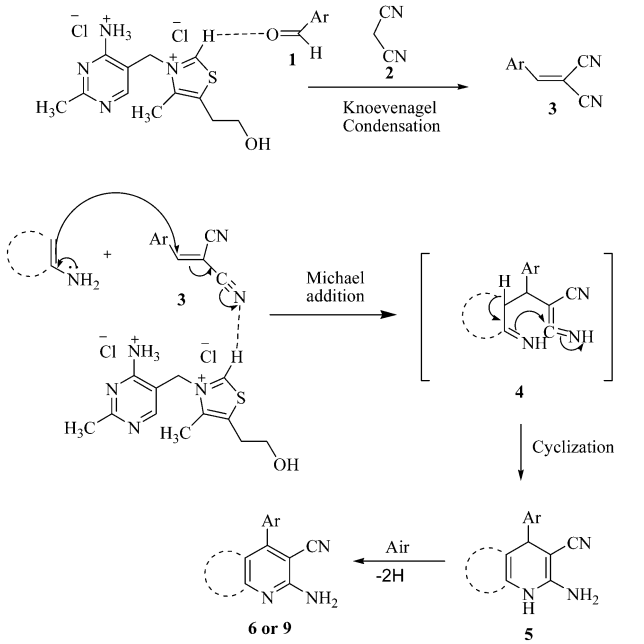
Entry	Aldehyde **1(a–h)**	Product **(9a–h)**[a]	Time (h)	Yield[b] (%)
1	 1a	 9a	2.5	95
2	 1b	 9b	2.5	95
3	 1c	 9c	2.5	95
4	 1d	 9d	2.5	94
5	 1e	 9e	2.0	95
6	 1f	 9f	2.0	95
7	 1g	 9g	2.0	94
8	 1h	 9h	2.5	94

[a] All products were characterized by IR, ^{1}H NMR, ^{13}C NMR and mass spectroscopy. [b] Isolated yield of pure product.

Thus water shows superiority over other solvents in terms of yield and reaction time. The reaction temperature was also examined and for this we carried out the same experiment in water under different temperature.

The reaction did not occur at room temperature (Table 3, entry 3) and gives a lower yield at low temperature (Table 3, entry 2). The best catalytic activity of VB1 was found at 90 °C.

To explore the scope and generality of the one-pot Knoevenagel condensation, Michael addition and cyclisation reaction, a range of pyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives were synthesized under optimized conditions (**6a–h**) using 6-aminouracil, malononitrile and different aldehydes. To extend the scope of this protocol, 6-aminouracil was replaced by 2-aminopyridine and the reaction was carried out under optimized conditions using



Scheme 3 Plausible mechanism of VB1-catalyzed synthesis of compounds **6** and **9**.

malononitrile and a variety of aldehydes, and the yields were found to be consistently good (**9a–h**) 92–94%. It was observed that the electronic nature of the substituent on the aromatic ring of aldehyde did not show any influence on the yield of product in both the cases, demonstrating the wide scope of this methodology. All the results are summarized in Tables 4 and 5.

On the basis of our observation, together with the literature survey,[7,9a] the formation of products **6** and **9** in this protocol may be rationalized by the initial formation of an intermediate cyanolefin **3** from the Knoevenagel condensation of aldehyde and malononitrile and subsequent Michael addition of 6-amino-1-methyluracil or 2-aminopyridine generates an intermediate **4** which was not isolable. This intermediate **4** undergoes intramolecular cyclization to give another intermediate **5** which converts into final product **6** or **9** *via* air oxidation[6,31,32] (Scheme 3).

Further we experimented with the reusability of VB1 because it is soluble in water and the product is insoluble. At the end of the reaction (as monitored by TLC) we isolated our desired product by simple filtration of the precipitate formed. The filtrate containing VB1 was again used in the reaction with model reactant giving 94, 91, 91% and 95, 93, 89% yields of products **6c** and **9c**, respectively, after 1–3 cycles. Thus the result of the study demonstrated that VB1 could be efficiently used as a recyclable catalyst for our three component reaction and it proves to be an ideal catalyst for MCR in organic synthesis with strong future potential. One clear advantage of the VB1–water system is that it yields very pure isolated products by simple filtration.

Conclusion

This described approach has many advantages like efficient and simple operation, better yield, non-hazardous reaction conditions, low cost and easily available starting materials. In this strategy, purification is not essential, avoiding the waste generated from column chromatography. More than this, we can say that herein we are giving details of a highly efficient, convenient, novel, rapid and very promising method with a diversity-oriented system for the synthesis of pyrido[2,3-*d*]pyrimidine, [1,8]-naphthyridine and their derivatives by using VB1 as a reusable catalyst in aqueous medium which has promising potential in the fields of chemical research and drug discovery.

Experimental

Materials and method

All chemical were reagent grade, purchased from Aldrich and Alfa Aesar and were used without purification. IR spectra were recorded on a Perkin Elmer – Spectrum RX-IFTIR spectrometer. NMR spectra were recorded on a BRUKER AVANCE II-400FT spectrometer (400 for ^{1}H NMR, 100 MHz for ^{13}C) using DMSO as solvent and TMS as an internal reference. Mass spectra were recorded on a JEOL SX-102 (FAB) mass spectrometer at 70 eV. Elemental analyses were carried out in a Coleman automatic carbon, hydrogen and nitrogen analyzer. All the reactions were monitored by TLC using precoated sheets of silica gel G/UV-254 of 0.25 mm thickness (Merck 60F_{254}). Melting points were determined by open glass capillary method and were uncorrected.

General procedure for the synthesis of 7-amino-2,4-dioxo-5-aryl-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile derivatives (6a–h). To a well-stirred solution of aromatic aldehyde **1** (1 equiv.) and malononitrile **2** (1 equiv.) in the presence of thiamine hydrochloride (10 mol%) in water (4 mL), 6-amino-1-methyluracil (1 equiv.) was added and the reaction mixture was heated at 90 °C for the stipulated time period. After completion of the reaction as monitored by TLC, the solid product was formed. The reaction mixture was cooled and the product was isolated by simple filtration.

General procedure for the synthesis of 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile derivatives (9a–h). To a well-stirred solution of aromatic aldehyde **1** (1 equiv.) and malononitrile **2** (1 equiv.) in the presence of thiamine hydrochloride (10 mol%) in water (4 mL), 2-aminopyridine (1 equiv.) was added and the reaction mixture was heated at 90 °C for the stipulated time period. After completion of the reaction as monitored by TLC, the solid product was formed. The reaction mixture was cooled and the product was isolated by simple filtration.

6a: 7-amino-1-methyl-5-(4-nitro-phenyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile. Red solid, Mp. > 300 °C; IR (KBr, cm^{-1}): 3607, 3534, 3297, 2222, 1703, 1590; ^{1}H NMR (400 MHz, DMSO): δ 3.87 (s, 3H) 7.58 (d, 2H, HAr, J = 8.6 Hz), 7.75 (brs, 2H, NH_2), 8.27 (d, 2H, HAr, J = 8.6 Hz), 11.55 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): δ 87.9, 98.2, 115.1, 122.9, 129.2, 144.0, 147.3, 150.2, 155.5, 156.6, 160.1, 160.8, 166.4; EIMS: (m/z): 338 (M^+), Anal. calcd for $C_{15}H_{10}N_6O_4$: C; 53.26, H; 2.98, N; 24.84; found C; 53.23, H; 2.97, N; 24.86.

6b: 7-amino-1-methyl-5-(2-chloro-phenyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile. White solid, Mp. > 300 °C; IR (KBr, cm^{-1}): 3390, 3311, 3188, 2228, 1699,

1648; ^{1}H NMR (400 MHz, DMSO): δ 3.9 (s, 3H), 7.28 (dd, 1H, HAr, J = 7.4, 1.5 Hz), 7.38 (t, 1H, HAr, J = 7.9 Hz), 7.43 (dt, 1H, HAr, J = 7.4, 1.5 Hz), 7.51 (d, 1H, HAr, J = 7.9 Hz), 7.75 (brs, 2H, NH_2), 11.55 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): δ 88.3, 98.5, 114.8, 126.9, 128.8, 129.0, 129.9, 130.5, 135.9, 150.1, 155.4, 155.8, 159.7, 160.9; EIMS: (m/z): 327 (M^+), Anal. calcd for $C_{15}H_{10}ClN_5O_2$: C; 54.97, H; 3.08, N; 21.37; found C; 54.99, H; 3.11, N; 21.39.

6c: 7-amino-1-methyl-5-(4-methoxy-phenyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile. Red solid, Mp. > 300 °C; (KBr, cm^{-1}): 3404, 3328, 3188, 2219, 1700, 1645; ^{1}H NMR (400 MHz, DMSO): δ 3.88 (s, 3H), 3.80 (s, 3H, OCH_3), 6.94 (m, 2H, H Ar), 7.19 (m, 2H, HAr), 7.57 (brs, 2H, NH_2), 10.73 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): δ 55.0, 88.8, 98.3, 112.9, 115.7, 128.6, 129.23, 150.1, 155.5, 158.8, 169.3, 160.0, 160.8; EIMS: (m/z): 323 (M^+), Anal. calcd for $C_{16}H_{13}N_5O_3$: C; 59.44, H; 4.05, N; 21.66; found C; 59.47, H; 4.03, N; 21.69.

6d: 7-amino-1-methyl-5-(3-hydroxy-phenyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile. Red solid, Mp. > 300 °C; IR (KBr, cm^{-1}): 3391, 3322, 3164, 2237, 1686, 1649; ^{1}H NMR (400 MHz, DMSO): δ 3.75 (s, 1H), 6.59 (s, 1H, HAr), 6.62 (d, 1H, HAr, J = 7.4 Hz), 6.78 (dd, 1H, HAr, J = 8.0, 1.9 Hz), 7.18 (t, 1H, HAr, J = 8.0 Hz), 7.58 (br s, 2H, NH_2), 9.46 (s, 1H, OH), 11.06 (s, 2H, 2NH); ^{13}C NMR (100 MHz, DMSO): δ 88.5, 98.3, 114.3, 115.2, 115.4, 118.1, 128.8, 137.9, 150.2, 155.4, 156.6, 159.0, 159.8, 160.8; EIMS: (m/z): 309 (M^+), Anal. calcd for $C_{15}H_{11}N_5O_3$: C 58.25, H 3.58, N 22.64; found C; 58.29, H; 3.55, N; 22.67.

6e: 7-amino-1-methyl-5-(3-nitro-phenyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile. Pale yellow solid Mp. > 300 °C; IR (KBr, cm^{-1}): 3384, 3321, 3172, 2216, 1718, 1662; ^{1}H NMR (400 MHz, DMSO): δ 3.81 (s, 3H), 7.75 (m, 2H, HAr), 7.77 (brs, 2H, NH_2), 8.19 (1H, HAr, J = 1.7 Hz), 8.29 (qd, 1H, HAr, J = 7.0, 1.1 Hz), 11.54 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): δ 88.3, 98.3, 115.2, 122.8, 123.1, 129.4, 134.4, 138.4, 147.1, 150.1, 155.5, 156.1, 160.2, 160.8; EIMS: (m/z): 338 (M^+), Anal. calcd for $C_{15}H_{10}N_6O_4$: C; 53.26, H; 2.98, N; 24.84; found C; 53.23, H; 2.99, N; 24.81.

6f: 7-amino-1-methyl-5-(phenyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile. White solid, Mp. > 300 °C; IR (KBr, cm^{-1}): 3403, 3331, 3174, 2224, 1707, 1643; ^{1}H NMR (400 MHz, DMSO): δ 3.79 (s, 3H), 7.24 (m, 2H, HAr), 7.40 (m, 3H, HAr), 7.59 (brs, 2H, NH_2), 11.44 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): δ 88.7, 98.3, 115.5, 127.5, 127.7, 128.3, 136.8, 150.3, 155.6, 159.0, 160.1, 160.9; EIMS: (m/z): 293 (M^+), Anal. calcd for $C_{15}H_{11}N_5O_2$: C; 61.43, H; 3.78, N; 23.88; found C; 61.45, H; 3.75, N; 23.92.

6g: 7-amino-1-methyl-5-(4-methyl-phenyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile. White solid, Mp. > 300 °C; IR (KBr, cm^{-1}): 3394, 3281, 3167, 2222, 1699, 16 459; ^{1}H NMR (400 MHz, DMSO): δ 3.81 (s, 3H), 2.36 (s, 3H, CH_3), 7.12 (d, 2H, HAr, J = 8.0 Hz), 7.20 (d, 2H, HAr, J = 8.0 Hz), 7.60 (br s, 2H, NH2), 11.43 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO) δ 20.9, 88.7, 98.3, 115.5, 127.5, 128.1, 133.7, 137.4, 150.1, 155.5, 159.1, 159.9, 160.8; EIMS: (m/z): 307 (M^+), Anal. calcd for $C_{16}H_{13}N_5O_2$: C; 62.53, H; 4.26, N; 22.79; found C; 62.56, H; 4.23, N; 22.81.

6h: 7-amino-1-methyl-5-(2,4-dichloro-phenyl)-2,4-dioxo-1,2,3,4-tetrahydro-pyrido[2,3-*d*]pyrimidine-6-carbonitrile. White solid, Mp. > 300 °C; IR (KBr, cm^{-1}): 3377, 3318, 3143, 2206, 1699, 1648; ^{1}H NMR (400 MHz, DMSO): δ 3.79 (s, 3H), 7.34 (d, 1H, HAr, J = 8.2 Hz), 7.50 (d, 1H, HAr, J = 8.2 Hz), 7.72 (brs, 1H, HAr), 7.81 (brs, 2H, NH2), 11.58 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO): δ 88.1, 98.4, 114.7, 127.2, 128.4, 130.3, 131.7, 133.7, 135.0, 150.1, 154.6, 155.4, 159.8, 160.9; EIMS: (m/z): 361 (M^+), Anal. calcd for $C_{15}H_9Cl_2N_5O_2$: C; 49.74, H; 2.50, N; 19.34; found C; 49.72, H; 2.53, N; 19.38.

9a: 2-amino-4-(4-nitrophenyl)-1,8-naphthyridine-3-carbonitrile. White solid, Mp. 159–162 °C; (KBr, cm^{-1}): 3265, 3326, 2226; ^{1}H NMR (400 Hz, DMSO): δ 7.16 (s, 2H, NH_2), 7.19 (m, 2HAr), 7.27 (m, 2HAr), 7.32 (m, 1HAr), 7.33 (m, 1HAr), 7.37 (m, 1HAr); ^{13}C NMR (100 MHz, DMSO): δ 111.1, 114.3, 116.8, 118.8, 122.3, 125.7, 128.5, 133.1, 136.5, 139.3, 142.5, 147.5, 148.4, 151.0 156.3, 164.3; EMIS: (m/z): 291.32 (M^+) Anal. calcd for $C_{15}H_9N_5O_2$: C; 61.85, H; 3.11, N; 24.04, O; 10.99. Found: C; 61.82, H; 3.13, N; 24.07, O; 10.98.

9b: 2-amino-4-(2-chloro-phenyl)-1,8-naphthyridine-3-carbonitrile. White solid Mp. 168–171 °C; IR (KBr, cm^{-1}): 3257, 3324, 2231. ^{1}H NMR (400 Hz, DMSO): δ 7.13 (s, 2H, NH_2), 7.17 (m, 1HAr), 7.21 (m, 1HAr), 7.33 (m, 1HAr), 7.36 (m, 1HAr), 7.38 (m, 1HAr), 7.41 (m, 1HAr), 7.44 (m, 1HAr); ^{13}C NMR (100 MHz, DMSO): δ 116.1, 119.3, 122.2, 123.1, 126.4, 129.3, 133.7, 136.1, 138.2, 142.0, 147.2, 149.4, 153.3, 157.1, 166.2, 169.4; EMIS: (m/z): 280 (M^+). Anal. calcd for $C_{16}H_{12}N_4$; C; 64.18, H; 3.23, N; 12.63. Found: C; 64.15, H; 3.22, N; 12.60.

9c: 2-amino-4(4-methoxy-phenyl)-1,8-naphthyridine-3-carbonitrile. White solid Mp. 156–158 °C; IR (KBr cm^{-1}): 3245, 3289, 2235. ^{1}H NMR (400 MHz, DMSO): δ 3.84 (s, 3H), 6.89 (m, 2H, HAr), 7.27 (m, 1HAr), 7.33 (m, 1HAr), 7.35 (s, 2H, NH_2), 7.39 (m, 2H, HAr), 7.43 (m, 1HAr); ^{13}C NMR (400 MHz, DMSO): δ 112.3, 117.6, 122.1, 124.0, 125.3, 128.4, 130.5, 134.7, 136.2, 142.0, 146.3, 147.4, 150.9, 152.2, 158.5, 168.3; EIMS: (m/z): 260 (M^+). Anal. calcd for $C_{16}H_{12}N_4$: C; 73.83, H; 4.65, N; 21.52. Found: C; 73.81, H; 4.66, N; 21.50.

9d: 2-amino-4-(3-hydroxyphenyl)-1,8-naphthyridine-3-carbonitrile. White solid, Mp. 162–164 °C; IR (KBr, cm^{-1}): 3251, 3312, 2225. ^{1}H NMR (400 MHz, DMSO): δ 7.17 (s, 2H, NH_2), 7.16 (s, 1HAr), 7.19 (m, 1HAr), 7.22 (m, 1HAr), 7.26 (m, 1HAr), 7.27 (m, 1HAr), 7.31 (m, 1HAr), 7.35 (m, 1HAr); ^{13}C NMR (100 MHz, DMSO): δ 105.6, 112.6, 116.2, 117.0, 118.9, 120.2, 121.4, 130.8, 139.4, 148.1, 152.1, 153.1, 160.1, 160.9, 161.7; EIMS: (m/z): 262 (M^+). Anal. calcd for $C_{15}H_{10}N_4O$: C; 68.69, H; 3.84, N; 21.36, found: C; 68.71, H; 3.83, N; 21.35.

9e: 2-amino-4-(3-nitrophenyl)-1,8-naphthyridine-3-carbonitrile. White solid, Mp. 160–162 °C; IR (KBr, cm^{-1}): 3249, 3311, 2234. ^{1}H NMR (400 MHz, DMSO): δ 7.19 (s, 2H, NH_2), 7.23 (s, 1HAr), 7.24 (m, 1HAr), 7.26 (m, 1HAr), 7.28 (m, 1HAr), 7.32 (m, 1HAr), 7.35 (m, 1HAr), 7.39 (m, 1HAr); ^{13}C NMR (100 MHz, DMSO): δ 111.5, 112.2, 113.9, 118.2, 122.4, 124.8, 129.2, 134.3, 136.5, 139.3, 142.3, 147.0, 149.2, 151.5, 155.2, 165.4; EIMS: (m/z): 291.41 (M^+). Anal. calcd for $C_{15}H_9N_5O_2$: C; 61.85, H; 3.11, N; 24.04, O; 10.99. Found: C; 69.85, H; 3.13, N; 24.03, O; 11.00.

9f: 2-amino-4-phenyl-1,8-naphthyridine-3-carbonitrile. White solid Mp. 152–155 °C; IR (KBr cm^{-1}): 3251, 3319, 2229. ^{1}H NMR

(400 Hz, DMSO): δ 7.10 (s, 2H, NH_2), 7.12 (m, 1HAr), 7.15 (m, 2HAr), 7.18 (m, 2HAr), 7.23 (m, 1HAr), 7.24 (m, 1HAr), 7.27 (m, 1HAr); ^{13}C NMR (100 MHz, DMSO): δ 118.2, 120.3, 124.1, 126.4, 127.2, 128.3, 129.1, 132.5, 136.0, 139.3, 143.4, 154.7, 158.5, 170.3, 171.2; EIMS: (*m*/*z*): 242 (M^+), Anal. calcd for $C_{15}H_{10}N_4$: C; 73.16, H; 4.09, N; 22.75. Found: C; 73.14, H; 4.07, N; 22.72.

9g: 2-amino-4-(4-methyl-phenyl)-1,8-naphthyridine-3-carbonitrile. White solid, Mp. 156–158 °C; IR (KBr, cm^{-1}): 3250, 3289, 2239. ^{1}H NMR (400 MHz, DMSO): δ 2.01 (s, 3H), 7.01 (s, 2H, NH_2), 7.11 (m, 2HAr), 7.14 (m, 2HAr), 7.17 (m, 1HAr), 7.20 (m, 1HAr), 7.24 (m, 1HAr); ^{13}C NMR (100 MHz, DMSO): δ 112.1, 117.0, 122.2, 124.3, 125.6, 128.4, 130.5, 134.3, 136.2, 142.3, 146.4, 147.7, 150.5, 152.3, 158.1, 168.0; EIMS: (*m*/*z*): 260 (M^+). Anal. calcd for $C_{16}H_{12}N_4$: C; 73.83, H; 4.65, N; 21.52. Found: C; 73.81, H; 4.66, N; 21.50.

9h: 2-amino-4-(2,4-dichlorophenyl)-1,8-naphthyridine-3-carbonitrile. White solid, Mp. 164–166 °C; IR (KBr, cm^{-1}): 3245, 3293, 2227. ^{1}H NMR (400 MHz, DMSO): δ 6.41 (s, 2H, NH_2), 6.86 (s, 1H), 6.79 (d, 1H, J = 8.4), 6.73 (d, 1H, J = 8.4), 6.75 (m, 1H), 6.82 (s, 1H), 6.77 (s, 1H, J = 8.2); ^{13}C NMR (100 MHz, DMSO): δ 109.8, 117.2, 118.9, 122.1, 127.5, 129.8, 130.9, 133.8, 134.2, 136.1, 136.8, 151.1, 161.8; EIMS: (*m*/*z*): 314 (M^+). Anal. calcd for $C_{15}H_8C_{l2}N_4$: C; 57.17, H; 2.56, N; 17.78, found: C; 57.15, H; 2.55, N; 17.80.

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