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3-Aminothieno[2,3-*b*]pyridine-2-carboxylate: Effective precursor for microwave-assisted three components synthesis of new pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one hybrids

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Abstract

In this study, ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate was taken as a versatile precursor for the one-pot three-component synthesis of related fused pyrimidine hybrids. The tandem protocol involved the reaction of 3-aminothieno[2,3-*b*]pyridine, dimethylformamide-dimethylacetal, and amines. The reaction afforded a new series of the target pyrimidine hybrids, linked to different arene units, in good to excellent yields. The prior reaction was evaluated in different solvents under traditional heating or microwave irradiation. Moreover, the influence of reaction temperature was also examined. The optimal conditions were obtained under microwave irradiation in dioxane at 110°C for 40 to 60 min. Additionally, by repeating the previous tandem reaction using the appropriate amines at reaction times of 20 to 60 min, a new series of pyrimidine hybrids linked to alkyl, arylthiazole, and benzo[*d*]thiazole units has been prepared in good to excellent yields. Furthermore, the utility of bis(amines) was examined to conduct the synthesis of new bis(pyrimidine) hybrids linked to aliphatic cores, in excellent yields, using the same protocol at 30 min reaction time.

1 | INTRODUCTION

Many attempts have been made recently to investigate the biological significance of pyrimidine hybrids. These hybrids demonstrated promising anticancer [1–3], antioxidant [4,5], antihypertensive [6,7], antiviral [8,9], antidiabetic [10,11], antiinflammatory [12–14], anti-ulcer [15], antibacterial [16–18], anti-influenza [19,20], and antimalarial activities [21,22]. Further, they exhibit powerful inhibitory activity to acetylcholinesterase, carbonic anhydrase [23], cyclooxygenase [24], and DNA gyrase enzymes [25].

Among the diverse spectrum of pyrimidine derivatives, those hybrids with related fused thienopyridine play an important role. Hence, pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidines can be considered as fluorene analogues with 5-thia-1,3,6-triaza subunits [26,27]. Because of the wide range of medicinal and pharmacological applications of the prior hybrids, several publications reported their synthesis [28–31]. These pyrimidine hybrids displayed the potent inhibitory activity to mGluR1, which plays a crucial role in the central sensitization of pain and other functions with potential implications for neurological and psychiatric conditions [32,33].

Moreover, pyridothienopyrimidines hybrids act as promising inhibitors of phosphodiesterase IV, a target for the treatment of asthma and chronic obstructive pulmonary disease [34]. They also act as potent and selective vascular endothelial growth factor receptor-2/kinase insert domain receptor kinase enzyme inhibitors [35], as well as inhibitors of multitarget Ser/Thr kinases [36].

In addition, these hybrids act as good antimicrobial [37,38], antifungal [39], anticancer [40], and antitumor agents [41]. Figure 1 represents some potent bioactive pyridothienopyrimidine hybrids **I–III** [32,35,38].

On the other hand, the rapid synthesis of biologically relevant heterocycles has remained one of the fascinating tasks for organic and medicinal chemists [42,43]. In recent years, multicomponent reactions have emerged as efficient methods for the synthesis of various polyfunctionalized heterocyclic hybrids, which involves the transformation of more than two reactants into the desired products in a one-pot one-step fashion [44,45]. Simplicity, shorter reaction time, greater efficiencies, improved atom economy, and minimizing the production of by-products with the generation of diverse and complex "drug-like" scaffolds linked to heterocyclic units are some of the advantages of these reactions [46,47].

In connection with our previous efforts in the multicomponent synthesis of biologically promising heterocyclic hybrids [48–55], we reported herein an efficient procedure for the synthesis of pyrimidine hybrids with related thieno[2,3-*b*]pyridine moiety.

2 | RESULTS AND DISCUSSION

The synthesis of pyrimidinone derivatives using 3-aminothieno[2,3-*b*]pyridine-2-carboxylate **I** was documented by Bohm et al. [56] via a three-step synthetic route (Scheme 1). At first, 3-aminothieno[2,3-*b*]pyridine-2-carboxylate **I** was heated in alcoholic potassium hydroxide solution to yield the potassium carboxylate **II**, which was cyclocondensed with acid anhydrides to give 2-alkyloxazinones **III**. Next, **III** was reacted with the primary amines to give the target pyrimidinones. In the current study, we designed a facile synthetic route to synthesize the target pyrimidinone hybrids utilizing a three-component one-pot protocol.

To begin our study, ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate derivative **1** was taken as a synthetic precursor for the tandem synthesis of related fused pyrimidine hybrids [57]. The three-component reaction between **1**, dimethylformamide-dimethylacetal (DMF-DMA) **2** and aniline **3a** was conducted as a model reaction to look for the optimal reaction conditions (Scheme 2) [32,58]. By conducting the prior reaction in

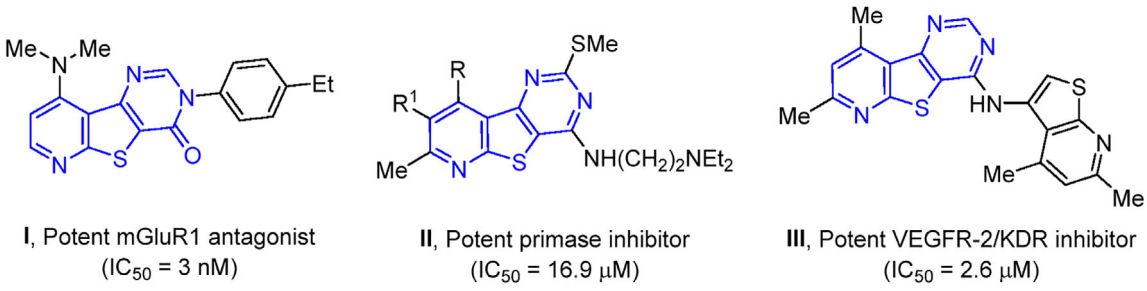
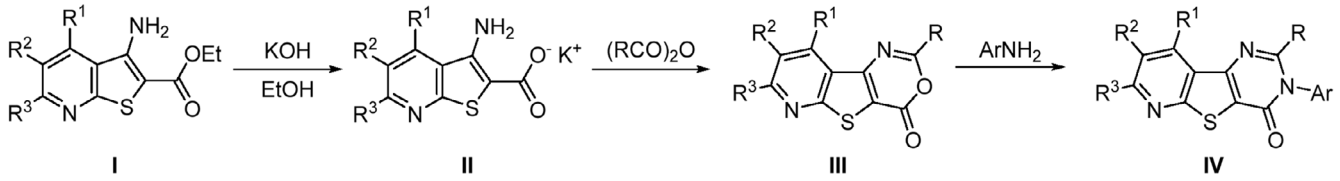
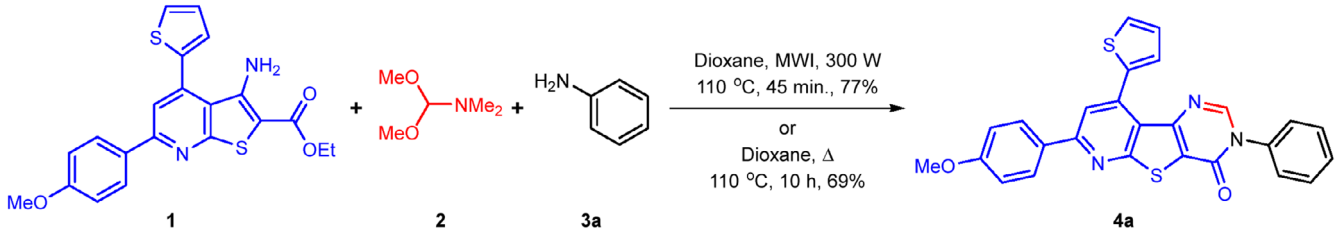


FIGURE 1 Structure of some potent bioactive pyridothienopyrimidine hybrids **I–III**



SCHEME 1 Previous synthesis of pyrimidinone hybrids



SCHEME 2 Tandem synthesis of pyrimidine hybrid **4a**

DMF under either conventional heating for 10 h or microwave irradiation for 45 min at 160 °C, the desired pyrimidine hybrid **4a** could be isolated in 52% and 64% yield, respectively (Table 1, entry 1). As a further investigation, we evaluated a series of different solvents including polar and nonpolar solvents (Table 1, entries 2–5). Moreover, the influence of reaction temperature was also examined (Table 1, entries 5–7). Thus, the microwave irradiation of the reaction mixture in dioxane as a solvent at 110°C was proved to be the best reaction conditions, providing the desired product in 77% yield.

Having determined the optimal conditions, we investigated the substrate scope of aryl amines **3a–3g** [58]. The results showed that aryl amines with various substituents could be well tolerated in this tandem cyclization reaction. As shown in Scheme 3, aryl amines **3b–3d** bearing electron-rich substituents (4-Me, 4-OMe, 4-Cl) were successfully transformed into the corresponding products **4b–4d** in good to excellent yields (82%–88%). Furthermore, aryl amines **3b–3d**, linked to electron-deficient substituents (4-CN, 4-NO_2, 4-CO_2Et), allowed the formation of the desired products **4e–4g** in moderate yields (57%–63%). Notably, as observed by thin layer chromatography analyses, the formation of pyrmidines **4b–4d** was conducted at a shorter reaction time (40 min) compared to the formation of **4f–4g** hybrids (60 min). These results implied that the stronger nucleophilicities of amines could be beneficial for the transformation. The structures of the pyrimidine hybrids **4** were established by considering of their spectral data and elemental analyses. The ^{1}H-nuclear magnetic resonance (NMR) spectrum of **4b**, as a representative example, revealed four singlet signals at δ 2.37, 3.84, 7.84, and 8.02 assigned to *p*-CH_3, *p*-OCH_3, pyridine-H, and pyrimidine-H protons, respectively. In addition, it showed a multiple signal in the range of δ 7.10–8.24 corresponding to the thiophene and aromatic protons (see Section 4).

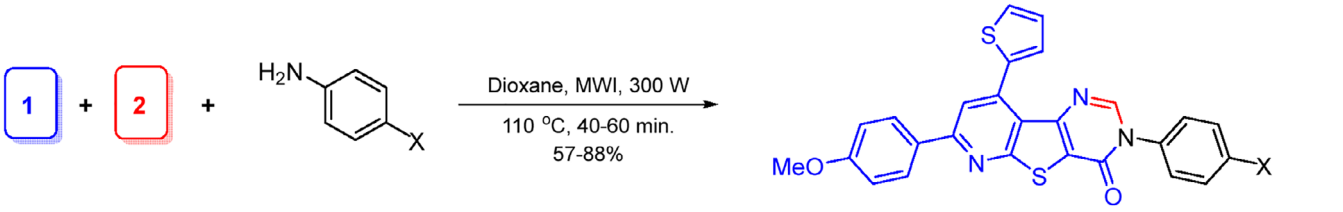
The prior tandem protocol was subsequently studied with a number of heteroaromatic amines to further demonstrate its generality. Conducting the reaction using a series of 4-arylthiazoles **5a–5e** gave the desired pyrimidine hybrids **6a–6e** in 77%–84% yields (see Scheme 4 and Section 4) [59].

The results showed that the reaction could readily employ a variety of aryl substituents, which are very significant functional units in pharmaceutical chemistry for post-diversification. It should be noted that the electronic effect and the position of the substituents on the phenyl rings seemed to affect this reaction somewhat, but not strongly, and the reactions of aromatic amines with

TABLE 1 Synthesis of pyrimidine hybrid **4a** under either microwave irradiation or conventional method

			Thermal heating[a,c]		Microwave irradiation [b,c]	
Entry	**Solvent**	**Temp. (°C)**	**Time (h)**	**Yield (%)**	**Time (min.)**	**Yield (%)**
1	DMF	160	10	52	60	64
2	Toluene	120	12	32	60	36
3	Xylene	140	12	37	60	40
4	Pyridine	120	10	57	45	65
5	Dioxane	110	10	69	45	77
6	Dioxane	rt	12	Traces	60	Traces
7	Dioxane	70	12	43	75	51

[a]The reactions were heated at reflux.
[b]The reactions were irradiated by microwaves of power 300 W at 120°C.
[c]The reactions were followed up by thin layer chromatography analyses.



3b, X = CH_3; **c**, X = OCH_3
d, X = Cl; **e**, X = CN
f, X = NO_2; **g**, X = COOEt

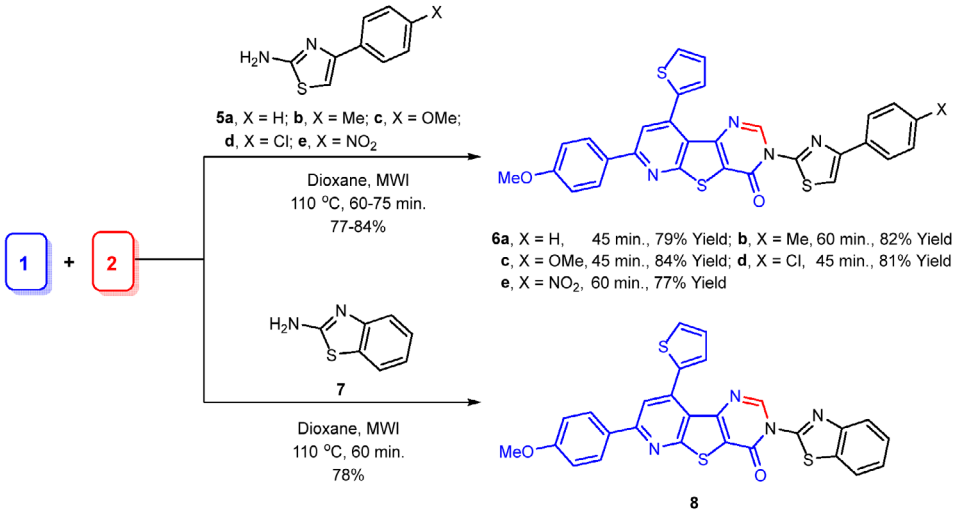
4b, X = CH_3, 40 min., 82% Yield; **c**, X = OCH_3, 40 min., 88% Yield
d, X = Cl, 40 min., 85% Yield; **e**, X = CN, 60 min., 60% Yield
f, X = NO_2, 60 min., 57% Yield; **g**, X = COOEt, 60 min., 63% Yield

SCHEME 3 Tandem synthesis of 3-arylpyrimidine hybrids **4b–4g**

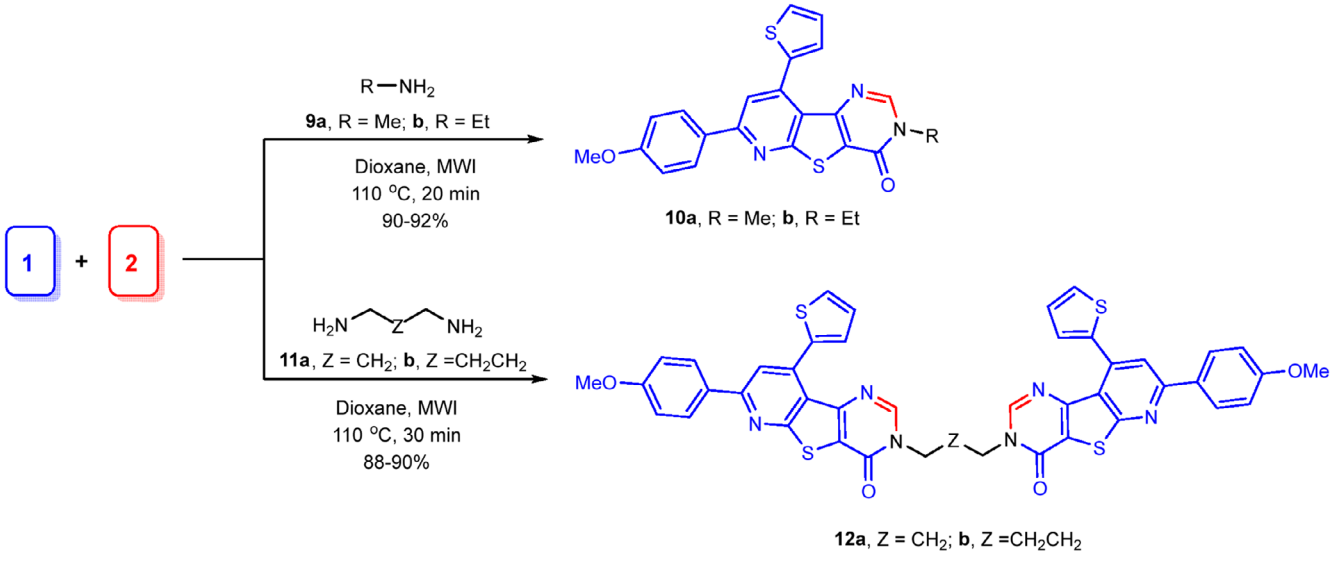
electron-rich substituents produced similar yields to those with electron-poor substituents. Furthermore, the desired pyrimidine hybrid **8** linked to benzo[*d*]thiazole unit was produced, in a good yield, by repeating the prior tandem protocol using benzo[*d*]thiazol-2-amine **7** as a reactive amine (Scheme 4) [60].

Next, we examined the utility of aliphatic amines in the formation of the target pyrimidine hybrids. Thus, the use of methylamine **9a** or ethylamine **9b** furnished the synthesis of hybrids **10a** and **10b**, respectively, in 90%–92% yields (Scheme 5) [61]. In order to improve the structural diversification of the product library, further extension of this reaction to different bis(pyrimidine) hybrids was performed. Thus, the use of bis(amines) **11a** or **11b** afforded the desired products in excellent yields (Scheme 5).

To identify the mechanism of the reaction, some control experiments were conducted (Scheme 6). Initially, 3-aminothieno[2,3-*b*]pyridine **1** was treated with DMF-DMA **2** under the standard conditions for 15 min to produce the corresponding 3-(([dimethylamino]methylene) amino)thieno[2,3-*b*]pyridine **13** in a quantitative yield (Scheme 6, Experiment A) [62]. Subsequently, the reaction of the compound **13** with aniline **3a** under standard conditions for 30 minutes achieved the generation of the foreseen product **4a** in 78% yield (Scheme 6, Experiment B). Next, we examined the reaction of DMF-MDA **2** with aniline **3a** under the optimized reaction conditions for 15 minutes, and the formamidine derivative **14** was obtained in a quantitative yield (Scheme 6, Experiment C) [63]. Then, the formamidine derivative **14** was transformed into the target molecule **4a** in 75% yield through

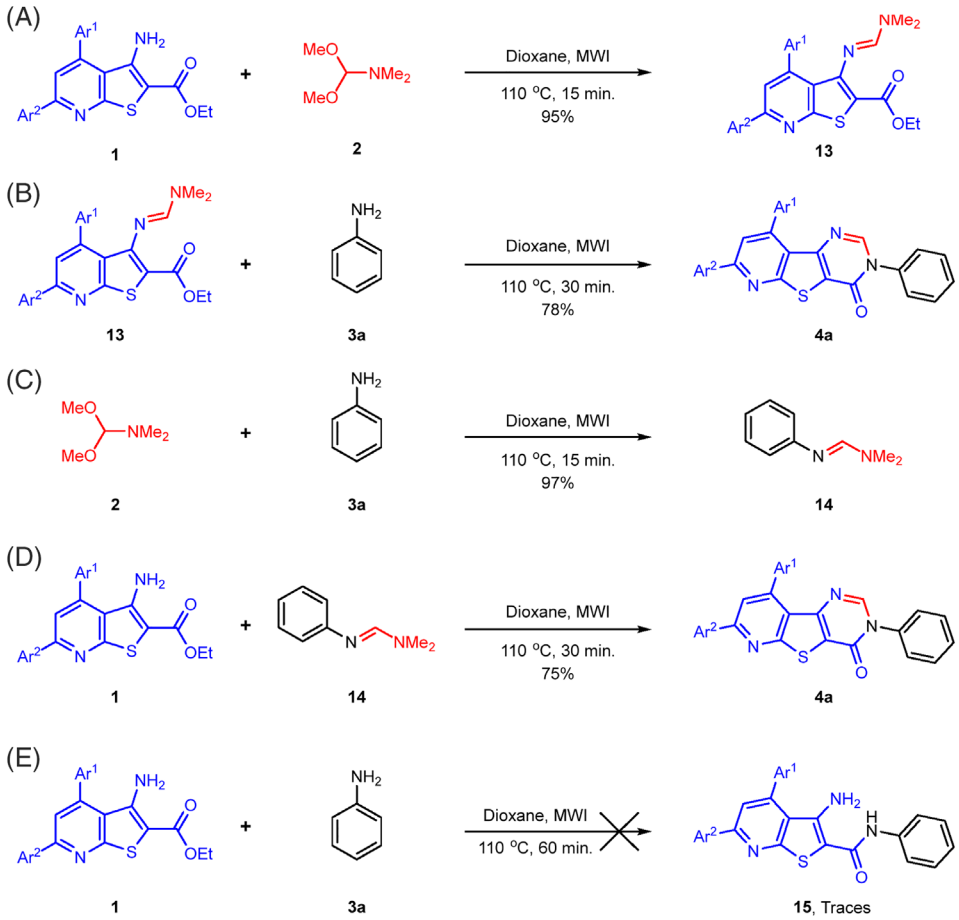


SCHEME 4 Tandem synthesis of pyrimidine hybrids **6** and **8**, linked to 4-arylthiazole or benzothiazole units



SCHEME 5 Tandem synthesis of 3-alkylpyrimidine hybrids **10** and bis(pyrimidine) hybrids **12**

SCHEME 6 Control experiments



its reaction with 3-aminothieno[2,3-*b*]pyridine **1** under the optimized reaction conditions for 30 min (Scheme 6, Experiment D). On the other hand, when the substrate **1** and the aniline **3a** were reacted in standard conditions for 60 min, compound **15** could not be detected (Scheme 6, Experiment E). This result suggested that the compound **15** was not an intermediate in the reaction.

Based on the above experimental results, a tentative reaction pathway is represented in Scheme 7. First, the corresponding formamidine intermediates **13** and **14** are formed via the condensation of DMF-DMA **2** with the appropriate substrate **1** or **3a**, respectively. Subsequently, two formamidine intermediates would undergo the cross-imidination followed by the cyclocondensation to give the desired product **4a** through the intermediate **16**.

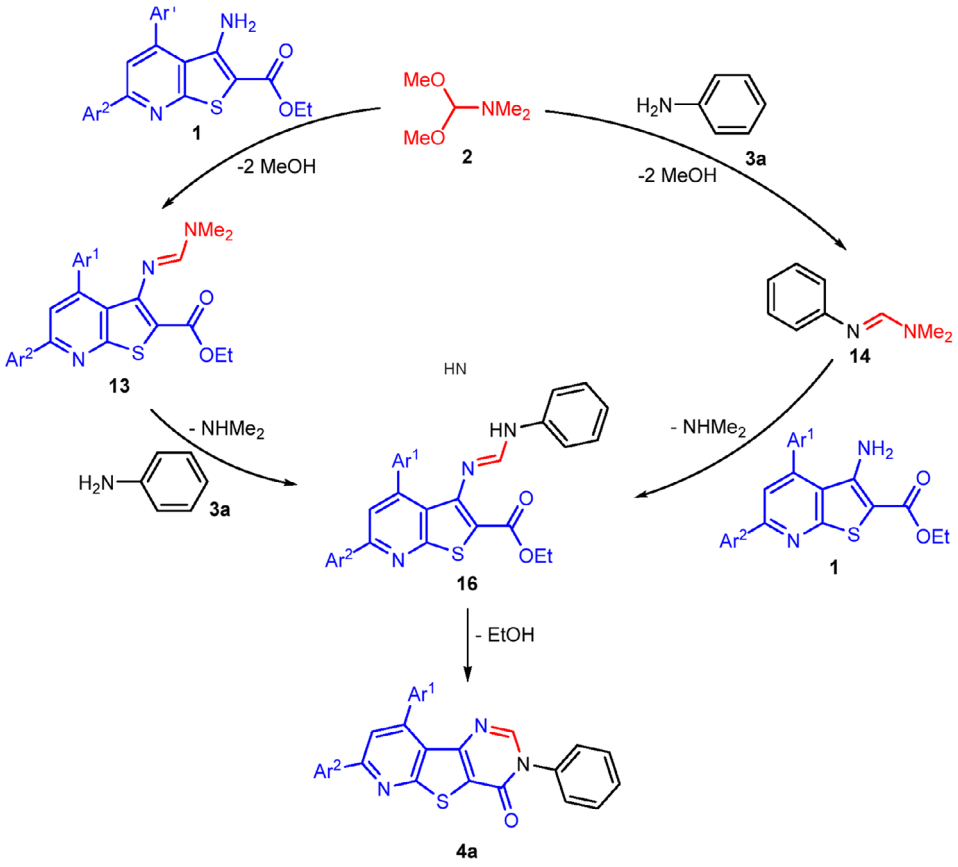
3 | CONCLUSIONS

We reported herein the development of an efficient one-pot three-component synthesis of a new series of pyrimidine hybrids with fused thieno[2,3-*b*]pyridine units. The tandem protocol involved the reaction of 3-aminothieno [2,3-*b*]pyridine, dimethylformamide-dimethylacetal and amines under microwave irradiation in dioxane at 110°C for 20–60 min. This work has demonstrated the construction of a series of pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one hybrids, linked to different alkyl, arene, arylthiazole and benzo[*d*]thiazole units in good to excellent yields.

4 | EXPERIMENTAL

4.1 | Materials

All solvents were acquired from commercial sources and used as received unless otherwise stated. All other chemicals were acquired from Merck or Aldrich and used without further purification. Microwave experiments were performed using chemistry, electronics and mechanics Discover apparatus (300 W), utilizing 35 ml capped glass reaction vessels automated power control based on temperature feedback. The melting points were measured on a Stuart melting point apparatus and are uncorrected. Infrared spectroscopy (IR) spectra were recorded on a Smart iTR, which is an ultra-high-performance, versatile attenuated total reflectance sampling



SCHEME 7 Suggested mechanism for the tandem synthesis of pyrimidine **4a**

accessory on the Nicolet iS10 fourier transform infrared spectroscopy spectrometer. NMR spectra were recorded on Bruker Avance III 400 MHz spectrophotometer (400 MHz for ^{1}H and 100 MHz for ^{13}C) using TMS as an internal standard and DMSO-d_6 as solvent and chemical shifts were expressed as δ ppm units. Elemental analyses were carried out on a EuroVector instrument C, H, N, S analyzer EA3000 Series.

4.2 | The procedures and spectral data

4.2.1 | General procedure for the synthesis of pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one hybrids 4, 6, 8 and 10

A mixture of ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate **1** (5 mmol), DMF-DMA **2** (6 mmol) and the appropriate of aryl amines **3a–3g**, 4-arylthiazoles **5a–5e**, benzo[*d*]thiazol-2-amine **7** or aliphatic amines **9a,b** (5 mmol) in dioxane (10 ml) was irradiated by microwaves with a power of 300 W to reach a reaction temperature of 110°C under autogenerated pressure for 20–60 min. The reaction mixture was cooled and then 2 ml of ethanol was added drop wisely. The product was collected by filtration, washed with cold ethanol, dried and then recrystallized from the proper solvent.

*7-(4-Methoxyphenyl)-3-phenyl-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (4a)*

Pale yellow solid (dioxane/ethanol mixture); Yield 1.80 g, 77%; m.p. 210–212°C; IR (υ cm^{-1}): 1665 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H, *p*-OCH$_3$), 7.08 (d, J = 8.8 Hz, 2H, ArH), 7.32 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.43 (d, J = 7.6 Hz, 2H, ArH), 7.54–7.60 (m, 3H, ArH), 7.82 (s, 1H, pyridine-H), 7.91 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.94 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.00 (s, 1H, pyrimidine-H), 8.22 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.8, 112.3, 114.2, 117.0, 126.4, 126.6, 127.8, 128.5, 128.7, 128.9, 129.4, 129.9, 130.4, 137.4, 137.7, 141.8, 148.2, 154.6, 156.5, 158.4, 158.9, 164.9; Anal. calcd. for $C_{26}H_{17}N_3O_2S_2$ (467.5): C, 66.79; H, 3.66; N, 8.99; found: C, 67.02; H, 3.43; N, 8.76%.

*7-(4-Methoxyphenyl)-9-(thiophen-2-yl)-3-(p-tolyl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (4b)*

Pale yellow solid (dioxane/ethanol mixture); Yield 1.97 g, 82%; m.p. 220°C; IR (υ cm^{-1}): 1667 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.37 (s, 3H, *p*-CH$_3$), 3.84 (s, 3H, *p*-OCH$_3$), 7.10 (d, J = 8.8 Hz, 2H, ArH), 7.20 (d, J = 8.0 Hz, 2H, ArH), 7.32 (t, J = 4.4 Hz, 1H, thiophene-

H4), 7.36 (d, J = 8.0 Hz, 2H, ArH), 7.84 (s, 1H, pyridine-H), 7.92 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.96 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.02 (s, 1H, pyrimidine-H), 8.24 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 20.8, 55.7, 112.7, 114.4, 117.2, 125.9, 126.3, 128.4, 128.7, 129.0, 129.7, 130.0, 130.7, 131.2, 135.3, 137.0, 142.1, 148.4, 154.2, 156.8, 158.7, 159.2, 164.4; Anal. calcd. for $C_{27}H_{19}N_3O_2S_2$ (481.5): C, 67.34; H, 3.98; N, 8.73; found: C, 67.59; H, 4.25; N, 8.47%.

3,7-Bis(4-methoxyphenyl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (4c)

Yellow solid (dioxane); Yield 2.19 g, 88%; m.p. 254–257°C; IR (υ cm^{-1}): 1668 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H, p-OCH$_3$), 3.85 (s, 3H, p-OCH$_3$), 7.05 (d, J = 8.4 Hz, 2H, ArH), 7.10 (d, J = 8.8 Hz, 2H, ArH), 7.34 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.38 (d, J = 8.4 Hz, 2H, ArH), 7.80 (s, 1H, pyridine-H), 7.93 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.96 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.01 (s, 1H, pyrimidine-H), 8.20 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.3, 55.7, 112.8, 114.2, 114.9, 117.5, 126.7, 127.0, 128.2, 128.5, 128.8, 129.6, 130.1, 130.8, 136.8, 141.3, 147.6, 153.7, 155.6, 156.2, 158.7, 159.3, 165.2; Anal. calcd. for $C_{27}H_{19}N_3O_3S_2$ (497.5): C, 65.17; H, 3.85; N, 8.44; found: C, 64.90; H, 3.59; N, 8.71%.

3-(4-Chlorophenyl)-7-(4-methoxyphenyl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (4d)

Pale yellow solid (dioxane); Yield 2.13 g, 85%; m.p. 258–260°C; IR (υ cm^{-1}): 1669 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H, p-OCH$_3$), 7.09 (d, J = 8.8 Hz, 2H, ArH), 7.34 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.45 (d, J = 8 Hz, 2H, ArH), 7.52 (d, J = 8 Hz, 2H, ArH), 7.85 (s, 1H, pyridine-H), 7.93 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.96 (d, J = 4.4 Hz, 1H, thiophene-H3), 7.99 (s, 1H, pyrimidine-H), 8.26 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.7, 111.9, 114.5, 117.4, 126.8, 128.4, 128.7, 128.9, 129.0, 129.5, 129.9, 130.4, 132.8, 136.0, 137.1, 142.4, 147.5, 153.9, 155.8, 158.7, 159.5, 165.4; Anal. calcd. for $C_{26}H_{16}ClN_3O_2S_2$ (502.0): C, 62.21; H, 3.21; N, 8.37; found: C, 61.95; H, 3.48; N, 8.56%.

4-(7-(4-Methoxyphenyl)-4-oxo-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-3(4H)-yl)benzonitrile (4e)

Yellow solid (dioxane); Yield 1.48 g, 60%; m.p. 244–247°C; IR (υ cm^{-1}): 2224 (CN), 1666 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H, p-OCH$_3$), 7.08 (d, J = 8.8 Hz, 2H, ArH), 7.32 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.69 (d, J = 8.0 Hz, 2H, ArH), 7.72 (d, J = 8.0 Hz, 2H, ArH), 7.83 (s, 1H, pyridine-H), 7.91 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.93 (d, J = 4.4 Hz, 1H, thiophene-H3), 7.97 (s, 1H, pyrimidine-H), 8.23 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.7, 103.6, 111.4, 114.3, 115.7, 117.1, 123.7, 127.2, 128.4, 128.8, 129.1, 129.7, 130.1, 133.5, 136.4, 138.4, 142.2, 148.0, 154.2, 156.3, 158.9, 159.2, 165.1; Anal. calcd. for $C_{27}H_{16}N_4O_2S_2$ (492.5): C, 65.84; H, 3.27; N, 11.37; found: C, 66.06; H, 3.02; N, 11.51%.

7-(4-Methoxyphenyl)-3-(4-nitrophenyl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (4f)

Yellow solid (dioxane); Yield 1.46 g, 57%; m.p. 278–280°C; IR (υ cm^{-1}): 1669 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.85 (s, 3H, p-OCH$_3$), 7.11 (d, J = 8.8 Hz, 2H, ArH), 7.35 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.81 (s, 1H, pyridine-H), 7.84 (d, J = 8.0 Hz, 2H, ArH), 7.95 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.98 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.04 (s, 1H, pyrimidine-H), 8.24 (d, J = 8.8 Hz, 2H, ArH), 8.30 (d, J = 8.0 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.6, 112.8, 114.5, 117.3, 124.3, 125.8, 126.8, 128.4, 128.7, 129.1, 129.9, 130.2, 136.9, 141.4, 141.7, 142.3, 147.6, 153.8, 155.9, 159.2, 159.6, 166.2; Anal. calcd. for $C_{26}H_{16}N_4O_4S_2$ (512.5): C, 60.93; H, 3.15; N, 10.93; found: C, 61.21; H, 3.00; N, 10.65%.

Ethyl 4-(7-(4-methoxyphenyl)-4-oxo-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-3(4H)-yl)benzoate (4 g)

Yellow solid (dioxane); Yield 1.70 g, 63%; m.p. 242–245°C; IR (υ cm^{-1}): 1731, 1667 (2 CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.39 (t, J = 7.2 Hz, 3H, CH_3CH$_2$), 3.85 (s, 3H, p-OCH$_3$), 4.36 (q, J = 7.2 Hz, 2H, CH$_3$CH_2), 7.10 (d, J = 8.8 Hz, 2H, ArH), 7.32 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.55 (d, J = 8.0 Hz, 2H, ArH), 7.81 (s, 1H, pyridine-H), 7.92 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.94 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.04 (s, 1H, pyrimidine-H), 8.09 (d, J = 8.0 Hz, 2H, ArH), 8.26 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 14.1, 55.8, 61.1, 112.5, 114.4, 117.1, 121.5, 123.9, 126.4, 128.5, 128.7, 128.9, 129.6, 129.9, 131.6, 136.5, 138.6, 142.2, 147.7, 154.2, 156.0, 159.1, 159.3, 164.3, 166.4 (CO); Anal. calcd. for $C_{29}H_{21}N_3O_4S_2$ (539.6): C, 64.55; H, 3.92; N, 7.79; found: C, 64.28; H, 4.13; N, 7.96%.

7-(4-Methoxyphenyl)-3-(4-phenylthiazol-2-yl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (6a)

Yellow solid (DMF/ethanol mixture); Yield 2.17 g, 79%; m.p. 240°C; IR (υ cm^{-1}): 1669 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.86 (s, 3H, p-OCH$_3$), 7.10 (d, J = 8.8 Hz, 2H, ArH), 7.34 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.41 (t, J = 7.6 Hz, 1H, ArH), 7.46 (t, J = 7.6 Hz, 2H, ArH), 7.77 (s, 1H, thiazole-H), 7.84 (s, 1H, pyridine-H), 7.88 (d,

J = 7.6 Hz, 2H, ArH), 7.94 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.97 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.03 (s, 1H, pyrimidine-H), 8.24 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.8, 112.2, 112.8, 114.6, 117.3, 126.3, 126.6, 128.2, 128.4, 128.7, 128.9, 129.3, 129.7, 130.2, 133.1, 137.0, 141.4, 147.3, 150.7, 152.4, 154.2, 155.8, 159.2, 160.2, 166.1; Anal. calcd. for $C_{29}H_{18}N_4O_2S_3$ (550.6): C, 63.25; H, 3.29; N, 10.17; found: C, 62.98; H, 3.54; N, 9.92%.

7-(4-Methoxyphenyl)-9-(thiophen-2-yl)-3-(4-(p-tolyl) thiazol-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4 (3H)-one (6b)

Yellow solid (DMF / ethanol mixture); Yield 2.31 g, 82%; m.p. 252–254°C; IR (υ cm^{-1}): 1667 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 2.39 (s, 3H, p-CH_3), 3.84 (s, 3H, p-OCH_3), 7.07 (d, J = 8.8 Hz, 2H, ArH), 7.29 (d, J = 8.0 Hz, 2H, ArH), 7.34 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.74 (s, 1H, thiazole-H), 7.82 (s, 1H, pyridine-H), 7.85 (d, J = 8.0 Hz, 2H, ArH), 7.95 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.97 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.06 (s, 1H, pyrimidine-H), 8.22 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 20.4, 55.7, 112.8, 113.0, 114.4, 116.9, 126.0, 126.4, 128.3, 128.6, 128.8, 129.0, 129.8, 130.5, 131.3, 136.7, 139.2, 141.7, 147.4, 151.0, 152.6, 153.8, 155.5, 159.0, 159.9, 165.8; Anal. calcd. for $C_{30}H_{20}N_4O_2S_3$ (564.7): C, 63.81; H, 3.57; N, 9.92; found: C, 64.05; H, 3.69; N, 10.20%.

7-(4-Methoxyphenyl)-3-(4-(4-methoxyphenyl)thiazol-2-yl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d] pyrimidin-4(3H)-one (6c)

Yellow solid (DMF/ethanol mixture); Yield 2.44 g, 84%; m.p. 272°C; IR (υ cm^{-1}): 1669 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.82 (s, 3H, p-OCH_3), 3.86 (s, 3H, p-OCH_3), 7.02 (d, J = 8.0 Hz, 2H, ArH), 7.07 (d, J = 8.8 Hz, 2H, ArH), 7.33 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.58 (d, J = 8.0 Hz, 2H, ArH), 7.80 (s, 1H, thiazole-H), 7.86 (s, 1H, pyridine-H), 7.93 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.96 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.02 (s, 1H, pyrimidine-H), 8.24 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.5, 55.8, 112.9, 113.2, 114.0, 114.6, 117.6, 126.5, 127.0, 128.1, 128.6, 128.8, 129.1, 129.7, 130.2, 136.3, 141.4, 147.0, 151.3, 152.3, 153.9, 156.2, 159.1, 159.4, 159.9, 166.3; Anal. calcd. for $C_{30}H_{20}N_4O_3S_3$ (580.7): C, 62.05; H, 3.47; N, 9.65; found: C, 61.79; H, 3.62; N, 9.83%.

3-(4-(4-Chlorophenyl)thiazol-2-yl)-7-(4-methoxyphenyl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (6d)

Yellow solid (DMF/ethanol mixture); Yield 2.37 g, 81%; m.p. 274–276°C; IR (υ cm^{-1}): 1666 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, p-OCH_3), 7.08 (d, J = 8.8 Hz, 2H, ArH), 7.32 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.49 (d, J = 8.0 Hz, 2H, ArH), 7.61 (d, J = 8.0 Hz, 2H, ArH), 7.81 (s, 1H, thiazole-H), 7.85 (s, 1H, pyridine-H), 7.96 (d, J = 2.4 Hz, 1H, thiophene-H5), 8.00 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.05 (s, 1H, pyrimidine-H), 8.17 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.7, 112.9, 113.6, 114.4, 116.6, 126.6, 127.6, 128.4, 128.6, 128.9, 129.2, 129.9, 130.4, 132.2, 135.9, 136.9, 142.1, 146.8, 150.9, 152.6, 154.4, 155.6, 159.3, 160.1, 166.4; Anal. calcd. for $C_{29}H_{17}ClN_4O_2S_3$ (585.1): C, 59.53; H, 2.93; N, 9.58; found: C, 59.80; H, 3.20; N, 9.32%.

7-(4-Methoxyphenyl)-3-(4-(4-nitrophenyl)thiazol-2-yl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (6e)

Yellow solid (DMF/ethanol mixture); Yield 2.29 g, 77%; m.p. 284–287°C; IR (υ cm^{-1}): 1667 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.83 (s, 3H, p-OCH_3), 7.09 (d, J = 8.8 Hz, 2H, ArH), 7.33 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.83 (s, 1H, thiazole-H), 7.86 (s, 1H, pyridine-H), 7.92 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.96 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.00 (s, 1H, pyrimidine-H), 8.09 (d, J = 8.0 Hz, 2H, ArH), 8.25 (d, J = 8.8 Hz, 2H, ArH), 8.30 (d, J = 8.0 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.6, 112.6, 113.1, 114.3, 117.0, 123.9, 126.2, 126.6, 128.6, 128.9, 129.2, 129.9, 130.6, 135.9, 137.4, 141.8, 147.6, 148.5, 151.2, 152.9, 154.6, 156.3, 159.4, 159.9, 166.3; Anal. calcd. for $C_{29}H_{17}N_5O_4S_3$ (595.6): C, 58.48; H, 2.88; N, 11.76; found: C, 58.21; H, 3.12; N, 11.98%.

3-(Benzo[d]thiazol-2-yl)-7-(4-methoxyphenyl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (8)

Pale yellow solid (dioxane); Yield 2.04 g, 78%; m.p. 276–278°C; IR (υ cm^{-1}): 1668 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 3.84 (s, 3H, p-OCH_3), 7.08 (d, J = 8.8 Hz, 2H, ArH), 7.32 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.37 (t, J = 7.6 Hz, 1H, H6′), 7.44 (t, J = 7.6 Hz, 1H, H5′), 7.82 (d, J = 7.6 Hz, 1H, H7′), 7.85 (s, 1H, pyridine-H), 7.89 (d, J = 7.6 Hz, 1H, H4′), 7.92 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.96 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.04 (s, 1H, pyrimidine-H), 8.26 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 55.7, 112.7, 114.5, 116.4, 120.5, 120.6, 123.3, 125.8, 126.6, 128.4, 128.7, 129.0, 129.8, 130.3, 132.2, 136.6, 141.8, 148.3, 151.8, 153.5, 154.4, 156.3, 158.1, 159.2, 165.8; Anal. calcd. for $C_{27}H_{16}N_4O_2S_3$ (524.6): C, 61.81; H, 3.07; N, 10.68; found: C, 62.02; H, 2.85; N, 10.42%.

7-(4-Methoxyphenyl)-3-methyl-9-(thiophen-2-yl)pyrido [3′,2′:4,5]thieno[3,2-d]pyrimidin-4(3H)-one (10a)

Pale yellow solid (dioxane/ethanol mixture); Yield 1.86 g, 92%; m.p. 188–190°C; IR (υ cm^{-1}): 1672 (CO); ^{1}H-NMR

(400 MHz, DMSO-d_6): δ 3.72 (s, 3H, NCH_3), 3.86 (s, 3H, *p*-OCH_3), 7.10 (d, J = 8.8 Hz, 2H, ArH), 7.35 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.86 (s, 1H, pyridine-H), 7.95 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.99 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.11 (s, 1H, pyrimidine-H), 8.26 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 32.1, 55.8, 113.1, 114.7, 116.8, 126.3, 128.6, 128.8, 129.1, 130.0, 130.5, 136.9, 142.4, 148.6, 154.8, 156.8, 158.7, 159.3, 165.4; Anal. calcd. for $C_{21}H_{15}N_3O_2S_2$ (405.4): C, 62.20; H, 3.73; N, 10.36; found: C, 61.95; H, 3.99; N, 10.21%.

*3-Ethyl-7-(4-methoxyphenyl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one (10b)*

Pale yellow solid (dioxane/ethanol mixture); Yield 1.89 g, 90%; m.p. 194–196°C; IR (υ cm^{-1}): 1673 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.34 (t, J = 7.2 Hz, 3H, NCH_2CH_3), 3.85 (s, 3H, *p*-OCH_3), 4.12 (q, J = 7.2 Hz, 2H, NCH_2CH_3), 7.08 (d, J = 8.8 Hz, 2H, ArH), 7.32 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.83 (s, 1H, pyridine-H), 7.94 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.97 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.13 (s, 1H, pyrimidine-H), 8.25 (d, J = 8.8 Hz, 2H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 13.4, 40.7, 55.7, 112.9, 114.6, 116.9, 126.5, 128.4, 128.7, 129.0, 129.9, 130.7, 136.6, 142.2, 148.3, 154.4, 156.3, 158.2, 159.5, 165.7; Anal. calcd. for $C_{22}H_{17}N_3O_2S_2$ (419.5): C, 62.99; H, 4.08; N, 10.02; found: C, 63.23; H, 3.87; N, 10.28%.

4.2.2 | General procedure for the synthesis of bis(pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one) hybrids 12

A mixture of ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate **1** (10 mmol), DMF-DMA **2** (12 mmol) and the appropriate of bis(amines) **11a,b** (5 mmol) in dioxane (10 ml) was irradiated by microwaves with a power of 300 W to reach a reaction temperature of 110°C under autogenerated pressure for 30 min. The reaction mixture was cooled and then 2 ml of ethanol was added drop wisely. The product was collected by filtration, washed with cold ethanol, dried and then recrystallized from the proper solvent.

*3,3′-(Propane-1,3-diyl)bis(7-(4-methoxyphenyl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one) (12a)*

Yellow solid (dioxane); Yield 3.62 g, 88%; m.p. 212–215°C; IR (υ cm^{-1}): 1670 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.92 (quint, J = 6.8 Hz, 2H, NCH_2CH_2), 3.84 (s, 6H, 2 *p*-OCH_3), 4.19 (t, J = 6.8 Hz, 4H, 2 NCH_2), 7.07 (d, J = 8.8 Hz, 4H, ArH), 7.33 (t, J = 4.4 Hz, 2H, 2 thiophene-H4), 7.83 (s, 2H, 2 pyridine-H), 7.95 (d, J = 2.4 Hz, 2H, 2 thiophene-H5), 7.99 (d, J = 4.4 Hz, 2H, 2 thiophene-H3), 8.14 (s, 2H, 2 pyrimidine-H), 8.24 (d, J = 8.8 Hz, 4H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 27.2, 43.5, 55.8, 113.2, 114.3, 116.5, 126.3, 128.6, 128.8, 129.0, 129.7, 130.4, 136.9, 142.0, 148.6, 154.3, 155.9, 158.7, 159.3, 165.2; Anal. calcd. for $C_{43}H_{30}N_6O_4S_4$ (822.9): C, 62.76; H, 3.67; N, 10.21; found: C, 62.99; H, 3.42; N, 9.97%.

*3,3′-(Butane-1,4-diyl)bis(7-(4-methoxyphenyl)-9-(thiophen-2-yl)pyrido[3′,2′:4,5]thieno[3,2-*d*]pyrimidin-4(3*H*)-one) (12b)*

Yellow solid (dioxane); Yield 3.77 g, 90%; m.p. 208–210°C; IR (υ cm^{-1}): 1671 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.70 (t, J = 6.8 Hz, 4H, 2 NCH_2CH_2), 3.85 (s, 6H, 2 *p*-OCH_3), 4.17 (t, J = 6.8 Hz, 4H, 2 NCH_2), 7.09 (d, J = 8.8 Hz, 4H, ArH), 7.34 (t, J = 4.4 Hz, 2H, 2 thiophene-H4), 7.83 (s, 2H, 2 pyridine-H), 7.93 (d, J = 2.4 Hz, 2H, 2 thiophene-H5), 7.95 (d, J = 4.4 Hz, 2H, 2 thiophene-H3), 8.13 (s, 2H, 2 pyrimidine-H), 8.26 (d, J = 8.8 Hz, 4H, ArH); ^{13}C-NMR (100 MHz, DMSO-d_6): δ 25.9, 45.2, 55.7, 113.5, 114.6, 116.7, 126.6, 128.5, 128.9, 129.2, 129.9, 130.8, 136.6, 141.8, 148.3, 153.9, 155.6, 158.4, 159.2, 164.8; Anal. calcd. for $C_{44}H_{32}N_6O_4S_4$ (837.0): C, 63.14; H, 3.85; N, 10.04; found: C, 62.87; H, 4.04; N, 9.76%.

*Synthesis of ethyl 3-(([dimethylamino]methylene)amino)-6-(4-methoxyphenyl)-4-(thiophen-2-yl)thieno[2,3-*b*]pyridine-2-carboxylate (13)*

A mixture of ethyl 3-aminothieno[2,3-*b*]pyridine-2-carboxylate **1** (5 mmol) and DMF-DMA **2** (6 mmol) in dioxane (10 ml) was irradiated by microwaves with a power of 300 W to reach a reaction temperature of 110°C under autogenerated pressure for 15 min. The reaction mixture was cooled and then 2 ml of ethanol was added drop wisely. The product was collected by filtration, washed with cold ethanol, dried and then recrystallized from dioxane/ethanol mixture as yellow solid; Yield 2.21 g, 95%; m.p. 182°C; IR (υ cm^{-1}): 1723 (CO); ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.32 (t, 3H, J = 7.2 Hz, CH_2CH_3), 3.07 (s, 3H, NCH_3), 3.17 (s, 3H, NCH_3), 3.85 (s, 3H, *p*-OCH_3), 4.26 (q, J = 7.2 Hz, 2H, CH_2CH_3), 7.08 (d, J = 8.8 Hz, 2H, ArH), 7.32 (t, J = 4.4 Hz, 1H, thiophene-H4), 7.41 (s, 1H, $CH=N(CH_3)_2$), 7.48 (d, J = 2.4 Hz, 1H, thiophene-H5), 7.77 (s, 1H, pyridine-H), 7.91 (d, J = 4.4 Hz, 1H, thiophene-H3), 8.20 (d, J = 8.8 Hz, 2H, ArH); Anal. calcd. for $C_{24}H_{23}N_3O_3S_2$ (465.5): C, 61.91; H, 4.98; N, 9.03; found: C, 62.13; H, 5.24; N, 8.77%.

DATA AVAILABILITY STATEMENT

The data that supports the findings of this study are available in the supplementary material of this article.

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