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Microwave-assisted efficient and convenient one-pot synthesis of novel 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)coumarins under solvent-free conditions

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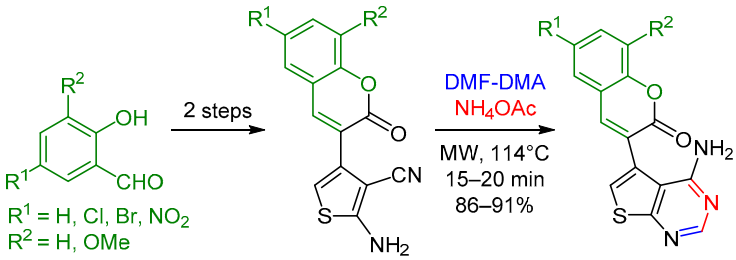


An efficient green synthesis of novel 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)coumarins has been developed. One-pot reaction of 3-acetylcoumarin, malononitrile, and elemental sulfur, catalyzed by L-proline, resulted in the formation of thiophene derivatives, which were used as precursors for the synthesis of 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)coumarins. Target compounds were prepared by a one-pot method or stepwise, and NH_4OAc was exploited as a reagent and molten salt. Microwave irradiation method was successfully applied to afford the products in excellent yields.

Keywords: ammonium acetate, coumarin, thieno[2,3-*d*]pyrimidine, green synthesis, microwave irradiation, solvent-free.

Coumarins (2*H*-chromen-2-ones) are valuable heterocycles that have been incorporated in many natural products with diverse pharmacological activities,[1] which make them suitable as potential building blocks for biologically active compounds containing coumarin–other heterocycle scaffold. Coumarin derivatives have been extensively utilized as therapeutic agents,[2] active media for tunable dye lasers,[3] fluorescence quenching agents,[4] luminescent probes,[5] and triplet sensitizers.[6]

As another versatile heterocycle, pyrimidine is an important motif that is commonly present in nucleic acids as nucleobases cytosine (C), thymine (T), and uracil (U). Fused pyrimidines continue to attract considerable attention of researchers in different fields because of their great practical utility, primarily, due to the wide spectrum of biological activities.[7] Accordingly, the pyrimidine ring has been fused to various heterocycles to obtain structurally diverse compounds, such as pyranopyrimidines,[8] pyridopyrimidines,[9] triazolopyrimidines,[10] pyrazolopyrimidines,[11] pyrimidoazepines,[12] coumarinopyrimidines,[13] furopyrimidines,[14] pyrrolopyrimidines,[15] thiazolopyrimidines,[16] and indolopyrimidines.[17]

Among the pyrimidine derivatives containing annulated five-membered heteroaromatic rings, thienopyrimidines occupy a special position. Thienopyrimidines are structural analogs of biogenic purines and can be considered as potential nucleic acid antimetabolites. Therefore, various aspects of the synthesis as well as chemical and biological properties of isomeric thienopyrimidines have been reviewed.[18–21] Keeping all the above considerations in mind, it seemed interesting to prepare a thieno[2,3-*d*]-pyrimidine ring with a coumarin motif in a single framework, which is structurally related to a nucleobase adenine (Fig. 1).

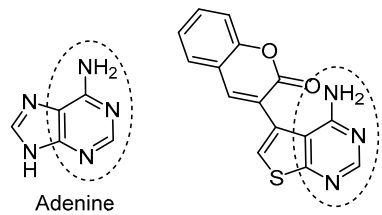
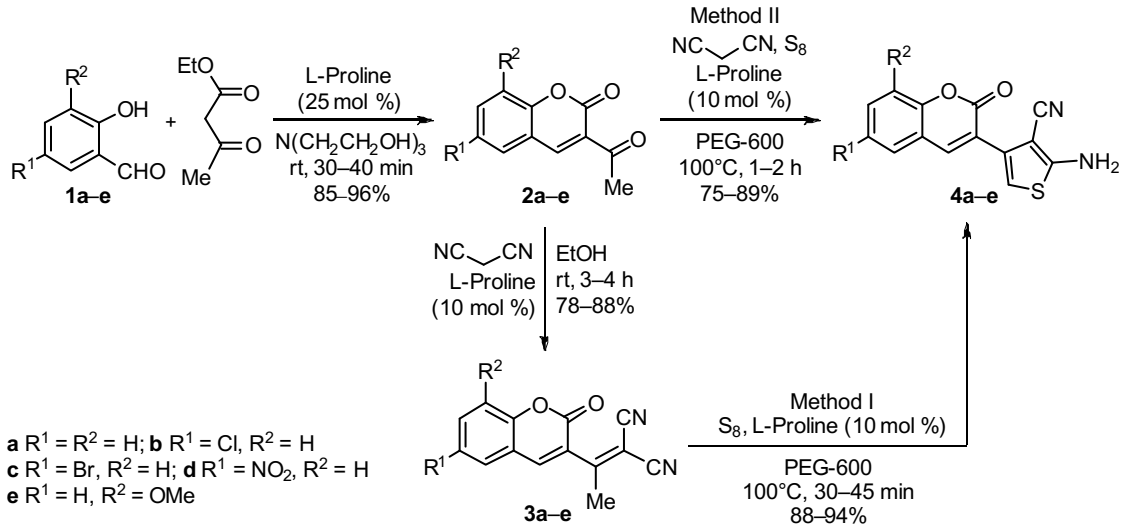


Figure 1. Structural similarity of nucleobase adenine and thieno-[2,3-*d*]pyrimidines.

Scheme 1



Thienopyrimidines can be synthesized from either pyrimidine[22] or thiophene[23] derivatives. However, since 1961, when the Gewald reaction was originally reported for the synthesis of 2-aminothiophenes, they have become invaluable precursors for obtaining thieno[2,3-*d*]pyrimidines.[24] Hussein reported the reaction of 3-acetyl-2*H*-benzo-[4,5]thiazolo[3,2-*a*]pyrimidin-2-one with malononitrile to afford ylidenemalononitrile, which upon the reaction with elemental sulfur provided the corresponding thiophene derivative.[25] The yield of product was increased by a one-pot reaction of acetyl compound, malononitrile, and elemental sulfur in refluxing EtOH containing triethylamine (TEA). Baell presented the synthesis of different thieno[2,3-*d*]pyrimidines by the reaction of 2-amino-4-(3,4-dimethoxyphenyl)-5-methylthiophene-3-carbonitrile and formamidine acetate at 160°C.[26] In addition, Al-Mousawi and Elnagdi reported the construction of pyrimidine ring in a reaction of ethyl 6-amino-5-cyano-4-phenyl-4*H*-pyran-3-carboxylate and *N*,*N*-dimethylformamide dimethyl acetal (DMF-DMA) in refluxing DMF to afford ethyl (*E*)-5-cyano-6-{[(dimethylamino)methylene]-amino}-4-phenyl-4*H*-pyran-3-carboxylate, which upon the cyclization with NH_4OAc in AcOH under reflux provided the corresponding pyrano[2,3-*d*]pyrimidine.[27]

Organocatalysis, as an approach for environmentally friendly synthesis, has become a rapidly growing field of chemistry. In this regard, L-proline has received much attention due to its dual role as a ligand[28] and catalyst.[29] However, development of benign catalytic procedures for the C=C and C–S bond formation reactions (Knoevenagel condensation and Gewald reaction, respectively) with high selectivity and yield of product is still desirable. Recently, L-proline has been successfully exploited in the Gewald reaction. Zeng et al. reported an efficient one-pot three-component protocol for the preparation of 2-aminothiophenes *via* the Gewald reaction catalyzed by L-proline.[30]

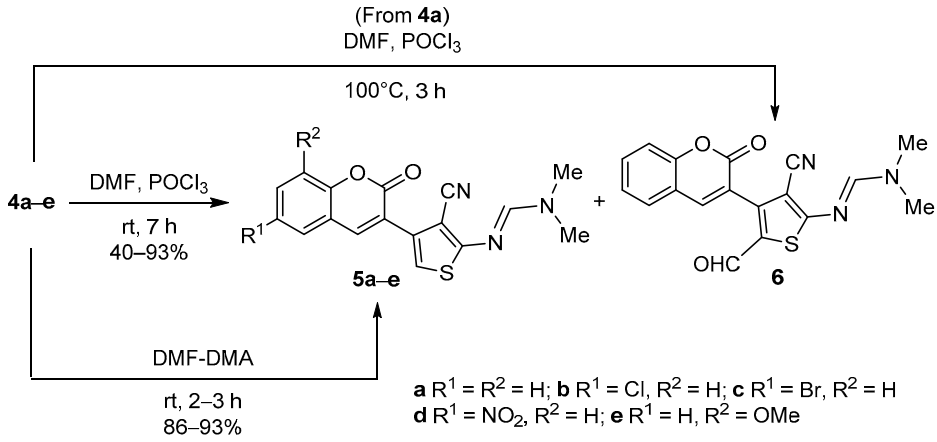
Since most of the chemical transformations take place in a solution, the role of solvents in organic synthesis is crucial. In general, any liquid can be utilized as a solvent. However, the ever-increasing awareness of environmental concerns and hazardous waste management has promoted development of greener synthetic methods. Obviously, an advanced chemical process would be performed under solvent-free conditions. As an alternative, H_2O,[31] perfluorinated hydrocarbons,[32] and supercritical fluids, in particular CO_2,[33] have been used to replace the conventional organic solvents that are often harmful and toxic. Molten salts and ionic liquids have been also evaluated as environmentally friendly solvents in both organic and organometallic chemistry.[34]

Based on the aforementioned information and in continuation of our earlier research on the synthesis of oxygen-containing heterocycles with a special reference to coumarins,[35–38] we report here a convenient method for the synthesis of 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)coumarins under solvent-free[39] conditions. The application of L-proline as an environmentally benign catalyst for the synthesis of differently substituted 2-amino-4-(2-oxo-2*H*-chromen-3-yl)-thiophene-3-carbonitriles has been also demonstrated.

The synthesis of 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)-coumarins commenced with the reaction of commercially available salicylaldehydes **1a**–**e** and ethyl acetoacetate using L-proline as a green catalyst and triethanolamine as a reaction media to give 3-acetylcoumarins **2a**–**e**[35] (Scheme 1). L-Proline can act both as acid and base[40] and thus facilitate the chemical transformations in a concerted manner, similar to enzymatic catalysis. The basic site of L-proline may induce the formation of a carbanion of the methylene compound, and the acidic site can activate the carbonyl group of aldehyde to promote the Knoevenagel condensation. Moreover, the acidic properties of the catalyst can facilitate the formation of pyran-2-one ring by an intramolecular transesterification.

The reaction of 3-acetylcoumarins **2a**–**e** and malononitrile in the presence of NH_4OAc in AcOH under reflux conditions for 9 h resulted in formation of the desired 2-[1-(2-oxo-2*H*-chromen-3-yl)ethylidene]malononitriles **3a**–**e** and also the undesired products of self-condensation of the starting materials **2a**–**e**, i.e., (*E*)-3,3'-(1-oxobut-2-ene-1,3-diyl)bis(2*H*-chromen-2-one) derivatives, some of which

Scheme 2



have been also reported by Bakeer.[41] Exploitation of other bases, such as piperidine, TEA, *N*,*N*-diisopropylethylamine (DIPEA), and 1,4-diazabicyclo[2.2.2]octane (DABCO), leaded to the same dimeric impurities. Therefore, L-proline was selected as a mild base and the reaction of 3-acetylcoumarins **2a**–**e** and malononitrile was conducted in EtOH to afford the corresponding 2-[1-(2-oxo-2*H*-chromen-3-yl)-ethylidene]malononitriles **3a**–**e** as the sole products.[36] Further heating compounds **3a**–**e** with elemental sulfur using L-proline (10 mol %) as a catalyst and polyethylene glycol 600 (PEG-600) as a solvent at 100°C provided the respective thiophene derivatives **4a**–**e**. Application of L-proline in the Gewald reaction was further explored for the possibility of a one-pot three-component synthesis of 2-amino-4-(2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitriles **4a**–**e**. Thus, equimolar amounts of starting material **2a**–**e**, malononitrile, and elemental sulfur in the presence of L-proline were heated in PEG-600 at 100°C for 1–2 h. As expected, the reaction was completed successfully to afford the desired products **4a**–**e** in high yields.

Subsequently, Vilsmeier–Haack formylation was performed with compound **4a** at room temperature for 7 h and resulted in the formation of two imidamide products, which were separated by column chromatography and identified as *N*'-[3-cyano-4-(2-oxo-2*H*-chromen-3-yl)thiophen-2-yl]-*N*,*N*-dimethylformimidamide (**5a**) and *N*'-[3-cyano-5-formyl-4-(2-oxo-2*H*-chromen-3-yl)thiophen-2-yl]-*N*,*N*-dimethylformimidamide (**6**) (Scheme 2). When the same chemical transformation was conducted at 100°C for 3 h, compound **6** was obtained as the sole product, whereas the reaction of DMF-DMA and thiophene **4a** at room temperature for 3 h exclusively provided the desired *N*,*N*-dimethylformimidamide **5a**. Thus, generalization of this method was further extended to other 2-amino-4-(2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitriles **4b**–**e**, and the corresponding imidamides **5b**–**e** were successfully synthesized.

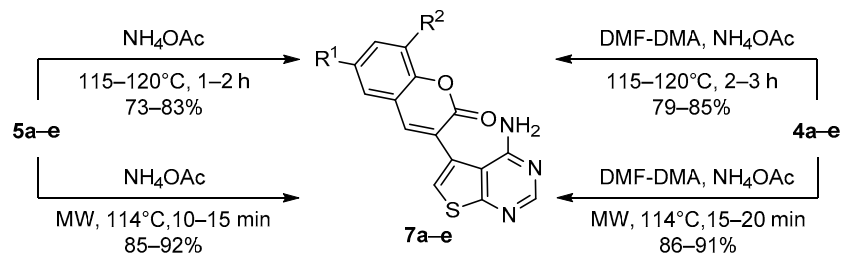
Further, reaction of imidamide **5a** and NH_4OAc was performed to obtain 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)-coumarin (**7a**) (Scheme 3). To optimize the reaction conditions and thereby ensure the highest yield of product **7a**, reaction of compound **5a** and NH_4OAc was examined in different solvents (Table 1). Protic solvents were screened, as the solubility of NH_4OAc was taken into consideration. In addition, solvent-free synthesis was also performed. Interestingly, the latter method was superior among the other tested conditions in terms of reaction time and yield of product **7a**.

Table 1. Optimization of the reaction conditions for the synthesis of compound **7a***

Solvent	Temperature, °C	Time, h	Yield of product **7a**, %
AcOH	Reflux	4	72
$EtCO_2H$	Reflux	4.5	65
HCO_2H	Reflux	4	69
H_2O	Reflux	15	33
MeOH	Reflux	6	58
EtOH	Reflux	6.5	55
i-PrOH	Reflux	7.5	49
n-BuOH	Reflux	12	44
–	114**	2	83

* Reaction conditions: imidamide **5a** (3.23 g, 10 mmol), NH_4OAc (2.31 g, 30 mmol), solvent (30 ml).
** Melting point of NH_4OAc.

Scheme 3



a $R^1 = R^2 = H$; **b** $R^1 = Cl$, $R^2 = H$; **c** $R^1 = Br$, $R^2 = H$; **d** $R^1 = NO_2$, $R^2 = H$; **e** $R^1 = H$, $R^2 = OMe$

Table 2. Yields of compounds **7a**–**e** synthesized from imidamides **5a**–**e** by conventional and microwave methods

Product	Conventional method*		Microwave method**	
	Time, h	Yield, %	Time, min	Yield, %
7a	1	83	12	91
7b	2	79	14	86
7c	1.5	75	10	85
7d	1.5	81	10	92
7e	2	73	15	87

* Reaction conditions: imidamide **5a**–**e** (10 mmol), NH_4OAc (2.31 g, 30 mmol), 115–120°C.
** Reaction conditions: imidamide **5a**–**e** (10 mmol), NH_4OAc (2.31 g, 30 mmol), MW, 114°C.

Table 3. Yields of compounds **7a**–**e** synthesized in a one-pot reaction from thiophenes **4a**–**e** by conventional and microwave methods

Product	Conventional method*		Microwave method**	
	Time, h	Yield, %	Time, min	Yield, %
7a	2.5	83	16	89
7b	2.5	80	18	90
7c	2	79	15	86
7d	2.5	83	17	87
7e	3	85	20	91

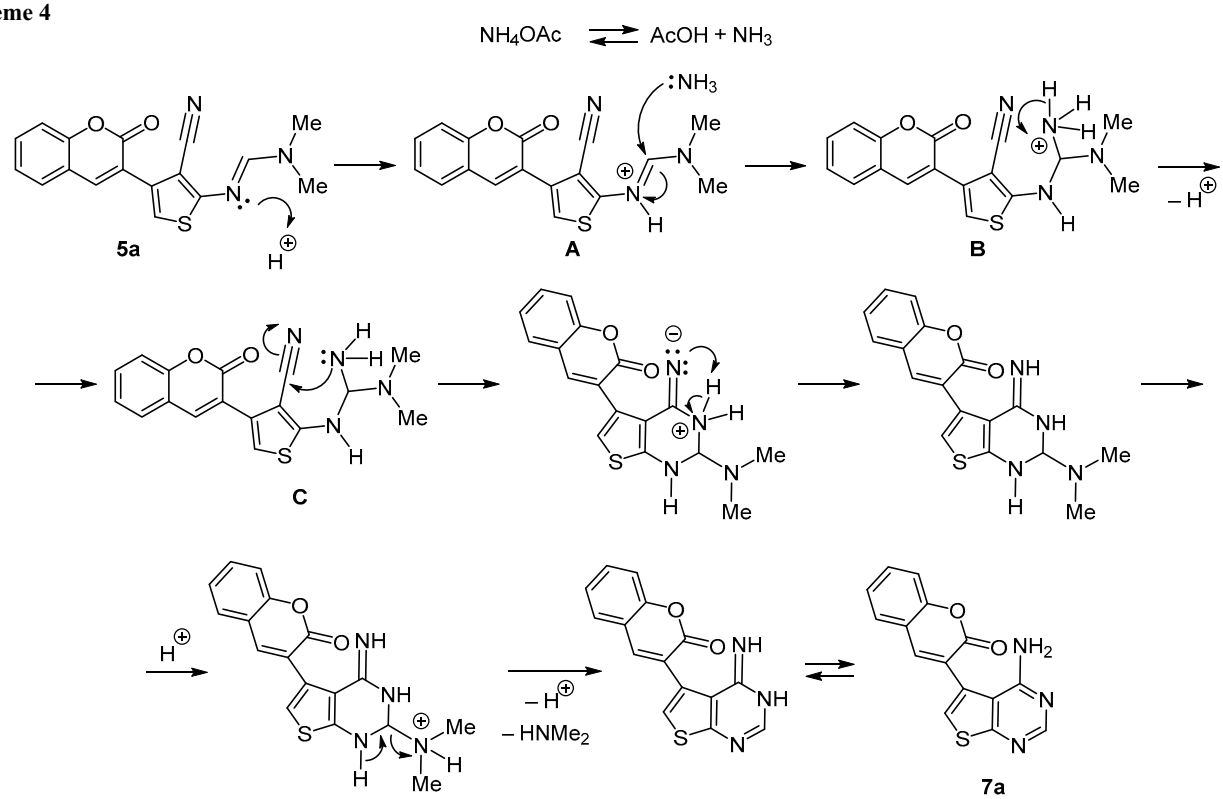
* Reaction conditions: thiophene **4a**–**e** (10 mmol), DMF-DMA (1.19 g, 10 mmol), NH_4OAc (2.31 g, 30 mmol), 115–120°C.
** Reaction conditions: thiophene **4a**–**e** (10 mmol), DMF-DMA (1.19 g, 10 mmol), NH_4OAc (2.31 g, 30 mmol), MW, 114°C.

The generality of this solvent-free reaction was studied by changing substrates **5b**–**e** which provided the respective products **7b**–**e** in high yields (Scheme 3, Table 2). Furthermore, the scope of the reaction was also executed under solvent-free conditions using microwave irradiation (MW). The results clearly indicate that both solvent-free approaches using conventional and MW heating are efficient. However, the remarkably shorter reaction times and higher yields of products **7a**–**e** make the microwave method superior.

Alternatively, 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)-coumarins **7a**–**e** could be prepared in a one-pot three-component reaction of thiophene derivatives **4a**–**e**, DMF-DMA, and NH_4OAc at 115–120°C for 2–3 h (Scheme 3, Table 3). As previously, microwave method was also successfully applied to obtain products **7a**–**e** in excellent yields. Structures of all compounds, synthesized by conventional and microwave-assisted methods, were confirmed by IR, ^1H and ^{13}C NMR spectroscopy and HRMS data.

The role of NH_4OAc as a molten salt in the synthesis of 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)coumarins **7a**–**e** has been evaluated. According to Kennedy, a molten salt may be one of the reactants or a catalyst and may also provide a unique ionic environment for the reaction.[42] Taking into account these considerations, a plausible mechanism for the formation of product **7a** from imidamide **5a** has been proposed (Scheme 4). At elevated temperatures, NH_4OAc may dissociate into AcOH and NH_3 and thereby act as a source of nitrogen for the construction of pyrimidine ring. Compound **5a** can abstract a proton from AcOH to generate a positive charge on the nitrogen atom and thus activate the imidamide moiety (intermediate **A**). The latter may then be attacked by NH_3 in a nucleophilic addition

Scheme 4



manner to generate intermediate **B**, which loses a proton to give compound **C**. The latter can undergo a cyclization process and AcOH-facilitated subsequent loss of dimethylamine molecule to afford the desired product **7a**.

In summary, solvent-free one-pot synthesis of novel 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)coumarins has been developed. For the first time, NH_4OAc has been used as a molten salt and reagent to carry out the reaction of 2-amino-4-(2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitriles and DMF-DMA at elevated temperatures. Both conventional and microwave methods allowed to obtain the desired compounds. In comparison to the conventional heating method, application of microwave irradiation proved to be an environmentally benign and noticeably faster, safer, and more efficient technique. Operational simplicity, solvent and catalyst-free, mild reaction conditions, nonchromatographic purification, and high yields of products are the advantages of this synthetic protocol.

Experimental

IR spectra were recorded on a PerkinElmer 1600 FTIR spectrometer using KBr pellets. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively) were acquired on a Varian 400 MHz spectrometer in DMSO-d_6 using TMS as internal standard. High-resolution mass spectra were recorded on an Agilent 1100 LCMS instrument using ESI method. Melting points were determined in open capillary tubes using hot H_2SO_4 bath and are uncorrected. TLC analyses were done on silica gel-G coated sheets supplied by Merck, and visualization was done using UV lamp and I_2. Microwave-assisted reactions were carried out in a household microwave oven with a maximum power of 800 W. All chemicals and solvents were obtained from commercial suppliers and were used without any purification.

Synthesis of 3-acetylcoumarins 2a–e (General method).[35] A mixture of salicylaldehyde **1a–e** (10 mmol), ethyl acetoacetate (1.56 g, 12 mmol), L-proline (288 mg, 25 mol %), and triethanolamine (5 ml) was stirred at room temperature for 30–40 min. Progress of the reaction was monitored by TLC (eluent EtOAc–hexane, 3:7). After completion of the reaction, the mixture was poured into ice-cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (20 ml), and air-dried. Crude product **2a–e** was recrystallized from a suitable solvent.

Synthesis of 2-ethylidenemalononitriles 3a–e (General method). A mixture of 3-acetylcoumarin **2a–e** (10 mmol), malononitrile (0.66 g, 10 mmol), L-proline (115 mg, 10 mol %), and EtOH (50 ml) was stirred at room temperature for 3–4 h. Progress of the reaction was monitored by TLC (eluent $CHCl_3$). After completion of the reaction, the mixture was poured into ice-cold H_2O (100 ml). The obtained solid was filtered off, washed with H_2O (2×50 ml), and air-dried. The crude product **3a–e** was recrystallized from a suitable solvent.

2-[1-(2-Oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (3a). Yield 2.02 g (86%), white solid, mp 162–164°C (MeOH) (mp 162–164°C (MeOH)[36]). IR spectrum, ν, cm^{-1}: 1728 (s, sh, C=O), 2238 (s, sh, C≡N), 2364 (s, sh, C≡N). ^{1}H NMR spectrum, δ, ppm: 2.62 (3H, s, CH_3); 7.36–7.62 (2H, m, H Ar); 7.70–7.92 (2H, m, H Ar); 8.50 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 23.4; 87.8; 112.6; 112.7; 116.9; 118.3; 124.4; 125.8; 130.2; 134.7; 145.5; 154.2; 157.3; 172.6. Found, *m*/*z*: 237.1288 $[M+H]^+$. $C_{14}H_9N_2O_2$. Calculated, *m*/*z*: 237.1292.

2-[1-(6-Chloro-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (3b). Yield 2.10 g (78%), white solid, mp 185–187°C (MeCN) (mp 185–187°C (MeCN)[36]). IR spectrum, ν, cm^{-1}: 1724 (s, sh, C=O), 2213 (s, sh, C≡N), 2376 (s, sh, C≡N). ^{1}H NMR spectrum, δ, ppm: 2.56 (3H, s, CH_3); 7.50–7.75 (2H, m, H Ar); 8.06 (1H, s, H Ar); 8.59 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 20.3; 82.8; 110.3; 114.7; 119.8; 120.3; 121.9; 125.2; 128.2; 131.8; 134.7; 150.8; 156.3; 169.9. Found, *m*/*z*: 271.0269 $[M+H]^+$. $C_{14}H_8ClN_2O_2$. Calculated, *m*/*z*: 271.0274.

2-[1-(6-Bromo-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (3c). Yield 2.75 g (88%), white solid, mp 203–205°C (EtOH) (mp 203–205°C (EtOH)[36]). IR spectrum, ν, cm^{-1}: 1728 (s, sh, C=O), 2122 (s, sh, C≡N), 2284 (s, sh, C≡N). ^{1}H NMR spectrum, δ, ppm: 2.55 (3H, s, CH_3); 7.48–7.74 (2H, m, H Ar); 8.05 (1H, s, H Ar); 8.58 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 22.5; 83.8; 110.8; 115.6; 119.1; 121.2; 122.5; 125.0; 128.5; 132.3; 135.1; 151.8; 158.2; 173.1. Found, *m*/*z*: 314.9767 $[M+H]^+$. $C_{14}H_8BrN_2O_2$. Calculated, *m*/*z*: 314.9769.

2-[1-(6-Nitro-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (3d). Yield 2.27 g (81%), white solid, mp 138–140°C (MeOH) (mp 138–140°C (MeOH)[36]). IR spectrum, ν, cm^{-1}: 1720 (s, sh, C=O), 2156 (s, sh, C≡N), 2283 (s, sh, C≡N). ^{1}H NMR spectrum, δ, ppm: 2.53 (3H, s, CH_3); 7.45–7.75 (2H, m, H Ar); 8.00 (1H, s, H Ar); 8.53 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 25.6; 84.4; 110.3; 116.5; 119.3; 121.8; 125.2; 125.5; 129.1; 132.0; 132.4; 153.0; 158.5; 172.1. Found, *m*/*z*: 282.0512 $[M+H]^+$. $C_{14}H_8N_3O_4$. Calculated, *m*/*z*: 282.0514.

2-[1-(8-Methoxy-2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile (3e). Yield 2.12 g (80%), white solid, mp 171–173°C (MeOH) (mp 171–173°C (MeOH)[36]). IR spectrum, ν, cm^{-1}: 1711 (s, sh, C=O), 2138 (s, sh, C≡N), 2238 (s, sh, C≡N). ^{1}H NMR spectrum, δ, ppm: 2.62 (3H, s, CH_3); 3.98 (3H, s, OCH_3); 7.36–7.52 (3H, m, H Ar); 8.56 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 19.8; 56.6; 82.5; 113.0; 113.3; 113.8; 119.8; 120.3; 125.3; 125.7; 131.8; 142.5; 148.8; 158.9; 172.5. Found, *m*/*z*: 267.0769 $[M+H]^+$. $C_{15}H_{11}N_2O_3$. Calculated, *m*/*z*: 267.0769.

Synthesis of thiophene derivatives 4a–e from 2-ethylidenemalononitriles 3a–e. Method I. A mixture of 2-[1-(2-oxo-2*H*-chromen-3-yl)ethylidene]malononitrile **3a–e** (10 mmol), elemental sulfur (0.32 g, 10 mmol), L-proline (115 mg, 10 mol %), and PEG-600 (30 ml) was stirred at 100°C for 30–45 min. Progress of the reaction was monitored by TLC (eluent MeOH–$CHCl_3$, 5:95). After completion of the reaction, the mixture was poured into ice-cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (2×20 ml), and air-dried. Crude product **4a–e** was recrystallized from a suitable solvent.

One-pot synthesis of thiophene derivatives 4a–e from 3-acetylcoumarins 2a–e. Method II. A mixture of 3-acetylcoumarin **2a–e** (10 mmol), malononitrile (0.66 g, 10 mmol),

elemental sulfur (0.32 g, 10 mmol), L-proline (115 mg, 10 mol %), and PEG-600 (30 ml) was stirred at 100°C for 1–2 h. Progress of the reaction was monitored by TLC (eluent MeOH–$CHCl_3$, 1:19). After completion of the reaction, the mixture was cooled to room temperature and then poured into ice-cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (2×50 ml), and air-dried. Crude product **4a**–**e** was recrystallized from a suitable solvent (see the characterization data of compounds **4a**–**e**).

2-Amino-4-(2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitrile (4a). Yield 2.51 (94%, method I), 2.38 g (89%, method II), yellow solid, mp 240–242°C (EtOH) (mp 240–242°C (EtOH)[36]). IR spectrum, ν, cm^{-1}: 1720 (s, sh, C=O), 2209 (s, sh, C≡N), 3290–3320 (m, br, NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.18 (2H, s, NH_2); 7.38 (1H, t, *J* = 4.8, H Ar); 7.45 (1H, d, *J* = 3.6, H Ar); 7.52 (1H, s, H thiophene); 7.60 (1H, t, *J* = 4.0, H Ar); 7.83 (1H, d, *J* = 8.0, H Ar); 8.50 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 81.8; 110.2; 116.5; 119.3; 121.8; 124.2; 126.5; 129.1; 132.0; 132.5; 145.8; 150.2; 153.2; 159.2. Found, *m*/*z*: 269.0378 $[M+H]^+$. $C_{14}H_9N_2O_2S$. Calculated, *m*/*z*: 269.0384.

2-Amino-4-(6-chloro-2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitrile (4b). Yield 2.70 g (90%, method I), 2.34 g (78%, method II), yellow solid, mp >250°C (MeCN) (mp >250°C (MeCN)[36]). IR spectrum, ν, cm^{-1}: 1702 (s, sh, C=O), 2213 (s, sh, C≡N), 3295–3330 (m, br, NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.98 (2H, s, NH_2); 7.20 (1H, d, *J* = 3.8, H Ar); 7.50 (1H, s, H thiophene); 7.83 (1H, d, *J* = 3.6, H Ar); 8.18 (1H, s, H Ar); 8.54 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 81.5; 113.5; 116.5; 119.1; 122.2; 122.5; 129.1; 129.5; 134.5; 140.8; 148.1; 151.0; 151.5; 159.8. Found, *m*/*z*: 302.9992 $[M+H]^+$. $C_{14}H_8ClN_2O_2S$. Calculated, *m*/*z*: 302.9987.

2-Amino-4-(6-bromo-2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitrile (4c). Yield 3.05 g (88%, method I), 2.76 g (80%, method II), yellow solid, mp 212–214°C (MeCN) (mp 212–214°C (MeCN)[36]). IR spectrum, ν, cm^{-1}: 1705 (s, sh, C=O), 2213 (s, sh, C≡N), 3280–3324 (m, br, NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 6.74 (1H, s, H thiophene); 7.20 (2H, s, NH_2); 7.56 (1H, d, *J* = 4.0, H Ar); 7.82 (1H, d, *J* = 4.8, H Ar); 8.14 (1H, s, H Ar); 8.64 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 83.3; 114.0; 116.3; 119.6; 121.8; 122.2; 128.4; 128.8; 134.9; 141.3; 149.3; 152.4; 152.7; 158.9. Found, *m*/*z*: 346.9489 $[M+H]^+$. $C_{14}H_8BrN_2O_2S$. Calculated, *m*/*z*: 346.9478.

2-Amino-4-(6-nitro-2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitrile (4d). Yield 2.78 g (89%, method I), 2.34 g (75%, method II), yellow solid, mp 128–130°C (MeOH) (mp 128–130°C (MeOH)[36]). IR spectrum, ν, cm^{-1}: 1738 (s, sh, C=O), 2248 (s, sh, C≡N), 3200–3265 (m, br, NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.22 (2H, s, NH_2); 7.46 (1H, s, H thiophene); 7.61 (1H, d, *J* = 3.8, H Ar); 8.13 (1H, d, *J* = 4.2, H Ar); 8.50 (1H, s, H Ar); 8.84 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 82.3; 110.6; 115.8; 118.3; 120.6; 120.9; 127.3; 127.7; 132.9; 140.6; 147.9; 151.4; 151.8; 157.9. Found, *m*/*z*: 314.0235 $[M+H]^+$. $C_{14}H_8N_3O_4S$. Calculated, *m*/*z*: 314.0236.

2-Amino-4-(8-methoxy-2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitrile (4e). Yield 2.68 g (90%, method I), 2.29 g (77%, method II), yellow solid, mp 147–149°C (EtOH) (mp 147–149°C (EtOH)[36]). IR spectrum, ν, cm^{-1}: 1734 (s, sh, C=O), 2161 (s, sh, C≡N), 3150–3200 (m, br, NH_2). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.96 (3H, s, OCH_3); 7.14 (2H, s, NH_2); 7.37 (1H, d, *J* = 4.2, H Ar); 7.42 (1H, d, *J* = 4.6, H Ar); 7.48 (1H, d, *J* = 3.8, H Ar); 7.52 (1H, s, H thiophene); 8.62 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 56.6; 84.2; 110.3; 114.7; 116.5; 119.8; 120.3; 121.9; 125.2; 131.8; 141.0; 142.5; 146.8; 158.9; 165.9. Found, *m*/*z*: 299.0412 $[M+H]^+$. $C_{15}H_{11}N_2O_3S$. Calculated, *m*/*z*: 299.0413.

Synthesis of imidamides 5a and 6. 2-Amino-4-(2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitrile (**4a**) (2.68 g, 10 mmol) was added to a solution of DMF (20 ml) and $POCl_3$ (10 ml) at 0–5°C. The reaction mixture was then stirred at room temperature for 7 h. Progress of the reaction was monitored by TLC (eluent EtOAc–hexane, 1:1). After completion of the reaction, the mixture was poured into ice-cold H_2O (60 ml). The obtained solid was filtered off, washed with H_2O (2×30 ml), and air-dried to obtain a mixture of products **5a** and **6** that were separated by column chromatography (silica gel, eluent EtOAc–hexane, 1:4).

(*E*)-*N*'-[3-Cyano-4-(2-oxo-2*H*-chromen-3-yl)thiophen-2-yl]-*N*,*N*-dimethylformimidamide (5a). Yield 1.81 g (56%), yellow solid, mp 228–230°C (EtOH). IR spectrum, ν, cm^{-1}: 1718 (s, sh, C=O), 2205 (s, sh, C≡N). ^1H NMR spectrum, δ, ppm: 3.08 (3H, s, CH_3); 3.19 (3H, s, CH_3); 7.20 (1H, s, H thiophene); 7.36–7.56 (2H, m, H Ar); 7.60–7.68 (1H, m, H Ar); 7.76–7.84 (1H, m, H Ar); 8.07 (1H, s, H-4); 8.27 (1H, s, N=CHN). ^{13}C NMR spectrum, δ, ppm: 34.0; 35.2; 109.2; 114.3; 115.8; 119.2; 120.2; 124.6; 128.8; 131.5; 134.4; 138.4; 143.3; 154.3; 158.7; 163.2. Found, *m*/*z*: 324.0807 $[M+H]^+$. $C_{17}H_{14}N_3O_2S$. Calculated, *m*/*z*: 324.0810.

(*E*)-*N*'-[3-Cyano-5-formyl-4-(2-oxo-2*H*-chromen-3-yl)-thiophen-2-yl]-*N*,*N*-dimethylformimidamide (6). Yield 1.40 g (40%), yellow solid, mp 164–166°C (acetone). IR spectrum, ν, cm^{-1}: 1720 (s, sh, C=O coumarin), 1738 (s, sh, C=O aldehyde), 2228 (s, sh, C≡N). ^1H NMR spectrum, δ, ppm: 3.10 (3H, s, CH_3); 3.21 (3H, s, CH_3); 7.38–7.84 (4H, m, H Ar); 8.30 (1H, s, H-4); 8.48 (1H, s, N=CHN); 9.63 (1H, s, CHO). Found, *m*/*z*: 352.0755 $[M+H]^+$. $C_{18}H_{14}N_3O_3S$. Calculated, *m*/*z*: 352.0748.

Synthesis of imidamides 5a–**e** (General method). A mixture of 2-amino-4-(2-oxo-2*H*-chromen-3-yl)thiophene-3-carbonitrile **4a**–**e** (10 mmol) and DMF-DMA (1.19 g, 10 mmol) was stirred at room temperature for 2–3 h. Progress of the reaction was monitored by TLC (eluent EtOAc–hexane, 3:7). After completion of the reaction, the mixture was poured into ice-cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (2×30 ml), and air-dried. Crude product **5a**–**e** was recrystallized from a suitable solvent.

(*E*)-*N*'-[3-Cyano-4-(2-oxo-2*H*-chromen-3-yl)thiophen-2-yl]-*N*,*N*-dimethylformimidamide (5a). Yield 3.01 g (93%).

(*E*)-*N*'-[4-(6-Chloro-2-oxo-2*H*-chromen-3-yl)-3-cyano-thiophen-2-yl]-*N*,*N*-dimethylformimidamide (5b). Yield 3.17 g (89%), yellow solid, mp 182–184°C (acetone). IR spectrum, ν, cm^{-1}: 1721 (s, sh, C=O), 2210 (s, sh, C≡N). ^1H NMR spectrum, δ, ppm: 3.09 (3H, s, CH_3); 3.18 (3H, s,

CH_3); 7.22 (1H, s, H thiophene); 7.38–7.48 (1H, m, H Ar); 7.57–7.65 (1H, m, H Ar); 7.71–7.79 (1H, m, H Ar); 8.05 (1H, s, H-4); 8.26 (1H, s, N=CHN). ^{13}C NMR spectrum, δ, ppm: 34.5; 35.3; 110.1; 113.9; 115.4; 119.7; 120.3; 125.7; 128.9; 129.3; 133.8; 137.1; 142.8; 153.8; 157.9; 162.6. Found, *m*/*z*: 358.0417 $[M+H]^+$. $C_{17}H_{13}ClN_3O_2S$. Calculated, *m*/*z*: 358.0412.

(*E*)-*N*'-[4-(6-Bromo-2-oxo-2*H*-chromen-3-yl)-3-cyanothiophen-2-yl]-*N*,*N*-dimethylformimidamide (5c). Yield 3.44 g (86%), yellow solid, mp 168–170°C (MeCN). IR spectrum, ν, cm^{-1}: 1713 (s, sh, C=O), 2216 (s, sh, C≡N). ^{1}H NMR spectrum, δ, ppm: 3.07 (3H, s, CH_3); 3.15 (3H, s, CH_3); 7.21 (1H, s, H thiophene); 7.37–7.45 (1H, m, H Ar); 7.56–7.64 (1H, m, H Ar); 7.72–7.78 (1H, m, H Ar); 8.06 (1H, s, H-4); 8.27 (1H, s, N=CHN). ^{13}C NMR spectrum, δ, ppm: 34.8; 35.1; 110.1; 113.9; 115.1; 119.6; 120.4; 123.0; 127.9; 130.9; 134.0; 137.9; 143.8; 153.1; 158.3; 162.5. Found, *m*/*z*: 402.2123 $[M+H]^+$. $C_{17}H_{13}BrN_3O_2S$. Calculated, *m*/*z*: 402.2120.

(*E*)-*N*'-[3-Cyano-4-(6-nitro-2-oxo-2*H*-chromen-3-yl)-thiophen-2-yl]-*N*,*N*-dimethylformimidamide (5d). Yield 3.26 g (89%), yellow solid, mp 196–198°C (MeOH). IR spectrum, ν, cm^{-1}: 1711 (s, sh, C=O), 2207 (s, sh, C≡N). ^{1}H NMR spectrum, δ, ppm: 3.08 (3H, s, CH_3); 3.16 (3H, s, CH_3); 7.20 (1H, s, H thiophene); 7.38–7.47 (1H, m, H Ar); 7.56–7.63 (1H, m, H Ar); 7.73–7.78 (1H, m, H Ar); 8.07 (1H, s, H-4); 8.29 (1H, s, N=CHN). ^{13}C NMR spectrum, δ, ppm: 34.6; 35.0; 109.9; 113.6; 115.2; 119.2; 120.1; 123.9; 127.7; 131.6; 134.2; 137.7; 142.9; 153.1; 157.6; 162.7. Found, *m*/*z*: 369.0578 $[M+H]^+$. $C_{17}H_{13}N_4O_4S$. Calculated, *m*/*z*: 369.0577.

(*E*)-*N*'-[3-Cyano-4-(8-methoxy-2-oxo-2*H*-chromen-3-yl)thiophen-2-yl]-*N*,*N*-dimethylformimidamide (5e). Yield 3.17 g (90%), yellow solid, mp 205–207°C (MeOH). IR spectrum, ν, cm^{-1}: 1717 (s, sh, C=O), 2221 (s, sh, C≡N). ^{1}H NMR spectrum, δ, ppm: 3.09 (3H, s, CH_3); 3.17 (3H, s, CH_3); 3.84 (3H, s, OCH_3); 7.22 (1H, s, H thiophene); 7.33–7.79 (3H, m, H Ar); 8.09 (1H, s, H-4); 8.28 (1H, s, N=CHN). ^{13}C NMR spectrum, δ, ppm: 34.2; 34.8; 55.6; 110.2; 113.7; 115.2; 119.6; 120.3; 123.5; 127.6; 130.9; 133.8; 138.4; 143.3; 153.6; 157.2; 164.1. Found, *m*/*z*: 354.0911 $[M+H]^+$. $C_{18}H_{16}N_3O_3S$. Calculated, *m*/*z*: 354.0912.

Synthesis of 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)-coumarins 7a–e from imidamides 5a–e (General method). A mixture of imidamide **5a–e** (10 mmol) and NH_4OAc (2.31 g, 30 mmol) was subjected to the conditions of conventional (the reaction mixture heated at 115–120°C for 1–2 h) or microwave (the reaction mixture irradiated in a microwave oven (800 W) at 114°C with 30% intensity for 10–15 min) method. Progress of the reaction was monitored by TLC (eluent MeOH–$CHCl_3$, 1:9). After completion of the reaction, the mixture was poured into ice-cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (2×30 ml), and air-dried. Crude product **7a–e** was recrystallized from a suitable solvent. Yields of compounds **7a–e** are given in Table 2.

One-pot synthesis of 3-(4-aminothieno[2,3-*d*]pyrimidin-5-yl)coumarins 7a–e from thiophene derivatives 4a–e (General method). A mixture of thiophene derivative **4a–e** (10 mmol), DMF-DMA (1.19 g, 10 mmol), and NH_4OAc (2.31 g, 30 mmol) was subjected to the conditions of conventional (the reaction mixture heated at 115–120°C for 2–3 h) or microwave (the reaction mixture irradiated in a microwave oven (800 W) at 114°C with 30% intensity for 15–20 min) method. Progress of the reaction was monitored by TLC (eluent MeOH–$CHCl_3$, 1:9). After completion of the reaction, the mixture was poured into ice-cold H_2O (50 ml). The obtained solid was filtered off, washed with H_2O (2 30 ml), and air-dried. Crude product **7a–e** was recrystallized from a suitable solvent. Yields of compounds **7a–e** are given in Table 3.

3-(4-Aminothieno[2,3-*d*]pyrimidin-5-yl)-2*H*-chromen-2-one (7a). Yellow solid, mp 193–195°C (MeOH). IR spectrum, ν, cm^{-1}: 1720 (s, sh, C=O), 3400–3442 (m, br, NH_2). ^{1}H NMR spectrum, δ, ppm: 6.81 (1H, s, H thiophene); 7.30 (2H, s, NH_2); 7.37–7.48 (3H, m, H Ar); 7.62–7.69 (1H, m, H Ar); 7.76–7.80 (1H, m, H-2); 8.27 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 119.4; 125.1; 126.0; 126.1; 126.4; 128.0; 129.3; 129.5; 129.9; 134.7; 135.6; 138.9; 156.7; 160.6; 166.6. Found, *m*/*z*: 296.0493 $[M+H]^+$. $C_{15}H_{10}N_3O_2S$. Calculated, *m*/*z*: 296.0494.

3-(4-Aminothieno[2,3-*d*]pyrimidin-5-yl)-6-chloro-2*H*-chromen-2-one (7b). Yellow solid, mp 225–227°C (EtOH). IR spectrum, ν, cm^{-1}: 1725 (s, sh, C=O), 3376–3432 (m, br, NH_2). ^{1}H NMR spectrum, δ, ppm: 6.84 (1H, s, H thiophene); 7.35 (2H, s, NH_2); 7.35–7.45 (2H, m, H Ar); 7.59–7.66 (1H, m, H Ar); 7.74–7.79 (1H, m, H-2); 8.30 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 119.2; 124.9; 125.8; 126.1; 126.3; 127.7; 129.1; 129.6; 129.8; 135.0; 135.3; 138.5; 156.1; 160.2; 165.7. Found, *m*/*z*: 330.0103 $[M+H]^+$. $C_{15}H_9ClN_3O_2S$. Calculated, *m*/*z*: 330.0104.

3-(4-Aminothieno[2,3-*d*]pyrimidin-5-yl)-6-bromo-2*H*-chromen-2-one (7c). Yellow solid, mp >250°C ($CHCl_3$). IR spectrum, ν, cm^{-1}: 1721 (s, sh, C=O), 3405–3454 (m, br, NH_2). ^{1}H NMR spectrum, δ, ppm: 6.83 (1H, s, H thiophene); 7.36 (2H, s, NH_2); 7.40–7.47 (2H, m, H Ar); 7.62–7.69 (1H, m, H Ar); 7.76–7.81 (1H, m, H-2); 8.28 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 119.6; 123.7; 125.1; 125.8; 126.2; 127.2; 129.5; 129.8; 130.2; 135.1; 135.6; 137.1; 155.8; 160.4; 166.0. Found, *m*/*z*: 373.9598 $[M+H]^+$. $C_{15}H_9BrN_3O_2S$. Calculated, *m*/*z*: 373.9599.

3-(4-Aminothieno[2,3-*d*]pyrimidin-5-yl)-6-nitro-2*H*-chromen-2-one (7d). Yellow solid, mp 208–210°C (EtOH). IR spectrum, ν, cm^{-1}: 1717 (s, sh, C=O), 3394–3445 (m, br, NH_2). ^{1}H NMR spectrum, δ, ppm: 6.81 (1H, s, H thiophene); 7.33 (2H, s, NH_2); 7.38–7.47 (2H, m, H Ar); 7.58–7.66 (1H, m, H Ar); 7.74–7.79 (1H, m, H-2); 8.27 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 119.3; 124.2; 125.2; 126.4; 126.7; 127.5; 128.7; 129.5; 129.9; 134.7; 135.2; 138.7; 155.6; 161.1; 166.6. Found, *m*/*z*: 341.0344 $[M+H]^+$. $C_{15}H_9N_4O_4S$. Calculated, *m*/*z*: 341.0344.

3-(4-Aminothieno[2,3-*d*]pyrimidin-5-yl)-8-methoxy-2*H*-chromen-2-one (7e). Yellow solid, mp 196–198°C (MeCN). IR spectrum, ν, cm^{-1}: 1728 (s, sh, C=O), 3426–3485 (m, br, NH_2). ^{1}H NMR spectrum, δ, ppm: 3.85 (3H, s, OCH_3); 6.85 (1H, s, H thiophene); 7.29 (2H, s, NH_2); 7.37–7.66 (3H, m, H Ar); 7.75–7.78 (1H, m, H-2); 8.31 (1H, s, H-4). ^{13}C NMR spectrum, δ, ppm: 55.6; 113.5; 119.3; 121.2;

123.5; 125.2; 125.7; 126.8; 128.1; 128.5; 129.1; 135.0; 138.5; 156.3; 160.2; 165.1. Found, *m*/*z*: 326.0599 $[M+H]^+$. $C_{16}H_{12}N_3O_3S$. Calculated, *m*/*z*: 326.0599.

A Supplementary information file containing IR, ^1H and ^{13}C NMR spectra and HRMS of compounds **2**–**5**, **7 a** is available at the journal website at http://link.springer.com/journal/10593.

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