



Efficient synthesis of novel chromenopyrido[3,2-e]isothiazolo[2,3-a]pyrimidines via a non-catalytic one-pot three-component reaction

Maryam Danehchin¹ · Abbas Ali Esmaeili¹

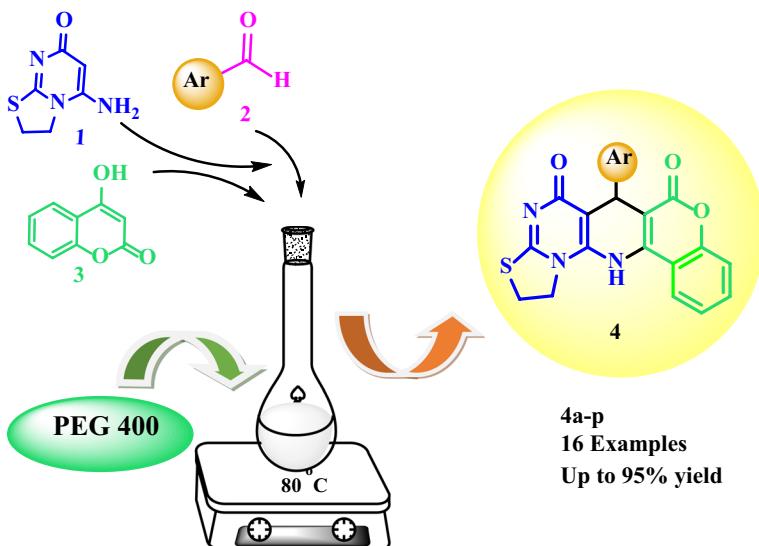
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Abstract

Herein, a novel series of chromenopyrido[3,2-e]isothiazolo[2,3-a]pyrimidines were synthesized by a three-component reaction of 4-hydroxy coumarin, aromatic aldehydes, and 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-a]pyrimidin-7-one under catalyst-free conditions in PEG 400 as a green solvent. The optimal reaction condition of this reaction was determined. The obtained product's structure was elucidated via NMR, IR, mass spectra, and elemental analysis techniques. This protocol has various advantages: excellent yields, short reaction times, no column chromatography, and green reaction media.

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Graphical abstract

Ar
= Aromatic, Polyaromatic

- PEG 400 as green solvent
- Mild reaction conditions
- Metal & catalyst free
- No column chromatography
- High yield

Keywords Fused-pyridothiazolopyrimidines · PEG-400 · 4-hydroxy coumarin · Catalyst-free · Three-component reaction

Introduction

In the last decade, green chemistry has significantly impacted several current areas, including catalyst and solvent-free syntheses, multicomponent reactions, and reactions in water or various other green solvents such as polyethylene glycol (PEG)

[1–7]. PEG is used in a range of organic reactions due to its unique properties, such as low cost, thermal stability, recyclability, non-volatility, and immiscibility with several numbers of organic solvents and biodegradable materials [8–13]. Multicomponent reactions (MCRs) provide an effective synthetic tool for synthesizing various and complex compounds in a single operation without isolating the intermediates from three or more reactants [14–19].

The fused heterocyclic compounds have attracted the most attention due to their engaging pharmacological and biological activities [20–24]. Polyfunctional heterocycles exist in the structure of many drugs. In recent years, much attention has been focused on synthesizing fused heterocyclic 1,4-dihydropyridine compounds owing to their remarkable application in numerous research areas, such as biological science and pharmaceutical chemistry [25, 26]. Dihydropyridine derivatives possess various biological activities such as vasodilator, a bronchodilator, geroprotective, antitumor, hepatoprotective, and antidiabetic activities [27–34]. In addition, dihydropyridine scaffolds are used in drugs such as nifedipine, amlodipine, nicardipine and are effective cardiovascular agents for treating hypertension [29–32, 35, 36]. Moreover, coumarin derivatives, which are fused with azaheterocycles, specifically pyridine nucleus, have been found to demonstrate antidiabetic, antiallergic, antioxidation, anti-osteoporotic effects, analgesic properties, and inotropic, chronotropic, and calcium antagonist activities (Fig. 1, A–C)[37–42]. These compounds have also

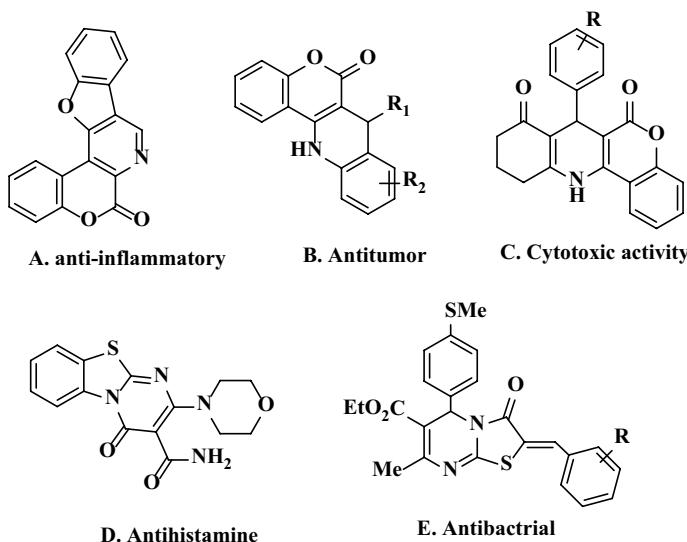
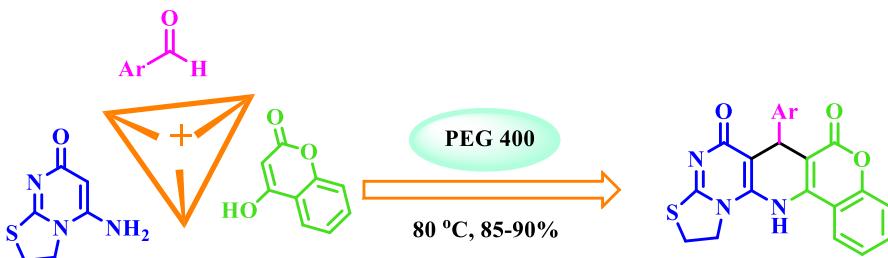


Fig. 1 Some biologically active thiazolopyrimidine and coumarin containing compounds

**Scheme 1** Adcdefghij

been used as photosensitizers in laser dyes, biological and medicinal fluorescent research areas [43, 44].

Furthermore, thiazolopyrimidine and its derivatives have become attractive due to their broad spectrum of biological effects, including anti-Parkinson, antibacterial, antihistamine, and antioxidant activities (Fig. 1, D and E) [45–54].

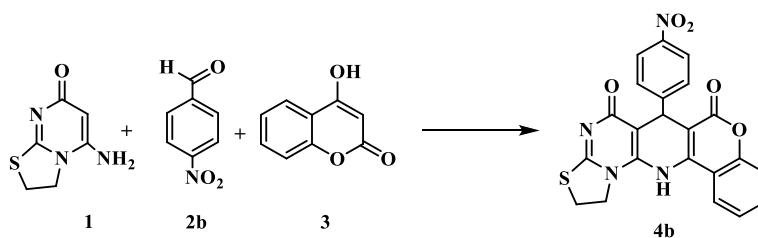
In recent years, synthetic chemists have reported many synthetic methods due to the biological and synthetic importance of coumarin–pyridine hybrids heterocycles [55–60]. Recently, Abu T. Khan and his group developed synthesizing pyrido[2,3-*c*] coumarin via a one-pot three-component reaction from a different substituent 3-amino-coumarins, phenylacetylenes and aromatic aldehydes [61]. In continuous, they synthesized chromeno[3,4-*b*]quinoline derivatives in the presence of a catalytic amount of *p*-toluene sulfonic acid (*p*-TSA) in ethanol [62]. Shortly after, Chen and his co-worker reported synthesizing a series of pyrido[2,3-*c*] coumarins derivatives from ketones, aromatic aldehydes, and 3-amino-coumarin using methane sulfonic acid catalyst [63]. Novel 7-aryl tetrahydro-chromeno[4,3-*b*]quinolin-6,8-diones were synthesized by R. Miri et al. from 4-hydroxycoumarin, dimedone, and aromatic aldehyde using ammonium acetate in benzene as solvent [39]. Adib et al. reported a method for synthesizing polysubstituted 5*H*-chromeno[4,3-*b*]pyridin-5-ones from 4-amino-coumarins and α -azido chalcones by using sodium hydroxide in DMF as solvent [64]. S. Pal and his co-workers reported the synthesis of functionalized dihydro chromeno[4,3-*b*]pyrazolo[4,3-*e*]pyridin-6(7*H*)-ones via a catalyzed-molecular iodine reaction of aldehydes derivatives, different 4-hydroxycoumarines and 3-amino-pyrazoles [65]. Similarly, Wang et al. developed a three-component reaction for the synthesis of substituted chromeno[4,3-*b*][1,5]naphthyridines from 4-hydroxycoumarin aryl aldehyde and 3-amino-pyridine in the presence of sulfamic acid as a catalyst in aqueous media [66].

As it turned out, in most of the previous works done by synthetic chemists to synthesize coumarin–pyridine hybrids derivatives, almost the same starting materials have been used under different conditions. They do not offer a high degree of substrate variability in most of them. Besides, they lack enough innovation, as 4-hydroxycoumarin was the critical substrate in all this literature.

Despite undeniable advantages, most methods mentioned above also suffer from disadvantages such as using metal catalysts, acids, bases, toxic solvents, multiple-step reaction sequences, complex workup, and separation techniques. Because of the above-mentioned biological properties, and in our ongoing effort to the synthesis of new coumarin-fused heterocyclic system [67–72], we herein report a facile and efficient green synthesis of a series of novel five-ring systems incorporating the coumarin-fused scaffold derivatives via a one-pot three-component tandem annulation reaction of 4-hydroxy coumarin,

Table 1 Optimization of reaction in various solvents and temperatures^a

Entry	Solvent ^b	Temperature (°C)	Time (h)	Yield (%) ^c
1	EtOH	Reflux	24	87
2	MeOH	Reflux	24	82
3	H ₂ O	Reflux	24	30
4	EtOH: H ₂ O (1:1)	Reflux	24	65
5	CH ₃ CN	Reflux	24	50
6	CH ₂ Cl ₂	r.t	24	20
7	n-butanol	Reflux	24	55
8	CHCl ₃	Reflux	24	10
9	neat	120	24	35
10	PEG 400	100	1.1	95
11	PEG 2000	100	24	75
12	PEG 4000	100	24	85
13	PEG 6000	100	24	70
14	Glycerol	100	24	25
15	Ethylene glycol	100	3	80
16	PEG 400	90	70	95
17	PEG 400	80	70	95
18	PEG 400	70	80	85

^aReaction conditions: All reactants [1, 2, 3(1 equivalent)] were mixed. ^bSolvent (0.5 mL). ^cIsolated yield

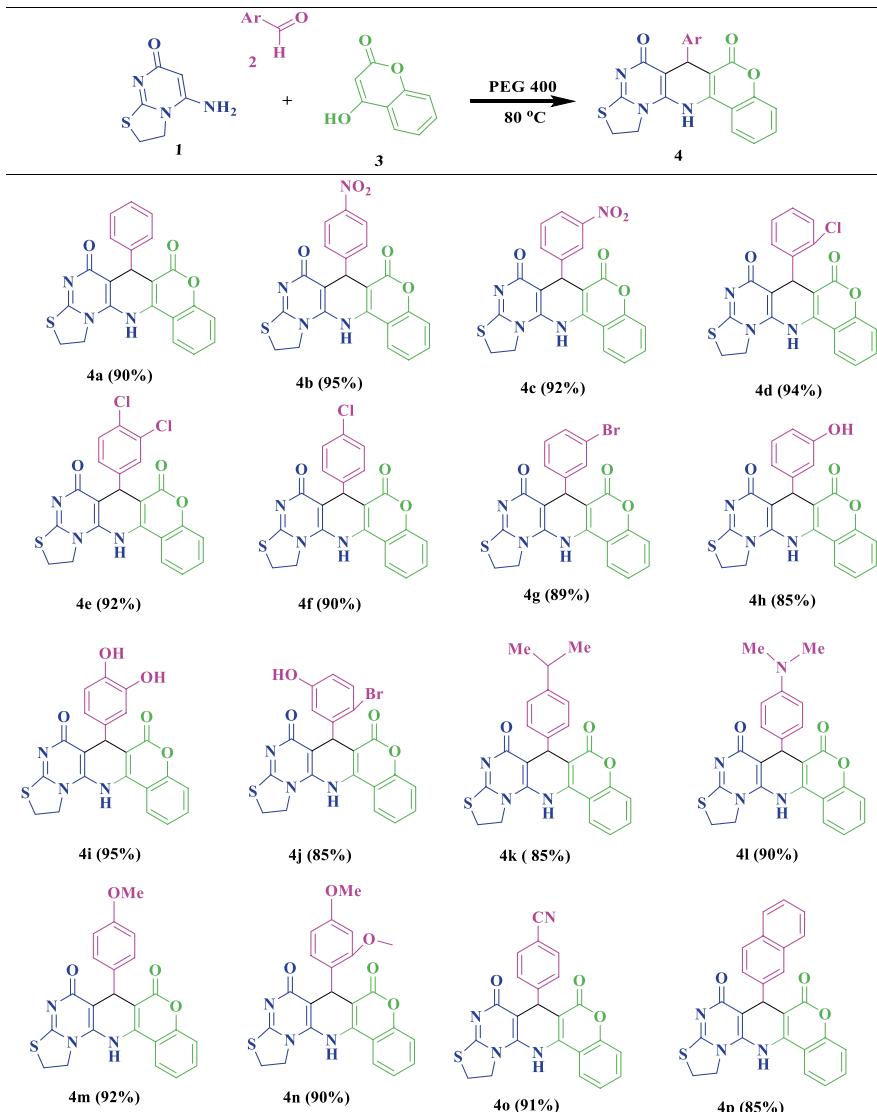
aromatic aldehydes and 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one as a heterocyclic fused amine in polyethylene glycol (PEG) as green solvent media (Scheme 1).

Results and discussion

We commenced our studies using 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one, 4-nitro benzaldehyde, and 4-hydroxycoumarine as the model substrates to screen the reaction conditions (Table 1). When the mixture of substrates in ethanol without any additives was stirred at reflux for 24 h, the expected product **4b** in 87% yield (Table 1, entry 1). To optimize the reaction condition, the model reaction was carried out in the various solvents including H₂O, EtOH/H₂O (1:1), MeOH, acetonitrile, dimethylsulfoxide (DMSO), dimethylformamide (DMF), n-butanol, CHCl₃, glycerol, ethylene glycol, and various polyethylene glycols (PEGs) with molecular weights 400, 2000, 4000, 6000 (Table 1, entry 2–8, 10–15). Interestingly, a significant improvement was observed, and the yield of **4b** increased to 95% using PEG 400 at 100 °C for 70 min (Table 1, entry 10). It was found that when the model reaction was performed at 120 °C for 24 h in solvent-free condition, a trace amount of product **4b** was provided (Table 1, entry 9).

Next, the effect of temperature was also evaluated for the model reaction in PEG 400. As shown in Table 1, the best result was obtained at 80 °C (Table 1, entry **16–18**). Finally, optimal condition was selected as **1**(1equiv), **2** (1equiv), **3** (1equiv) in PEG 400 (0.5 ml) at 80 °C for 70 min. Using optimized reaction conditions, the scope of the reaction was explored by a variety of aromatic aldehydes containing both electron-withdrawing and electron-donating groups such as (-Cl, -Br, -OCH₃, -OH, -N(CH₃)₂ and -CN) in various positions of the benzene ring of aromatic aldehydes, successfully converted to the corresponding products in high to excellent yields (Table 2). In addition, 2-naphthaldehyde also provided the desired product in an excellent yield (Table 2, 4p). Also, we next tested aliphatic aldehydes under the optimized reaction conditions, but unfortunately, no desired product was obtained.

Table 2: Synthesis of a library of coumarin fused pyridothiazolopyrimidine derivatives in PEG 400



Reaction condition: heterocyclic amine (1 mmole), 4-hydroxycoumarine (1 mmole) in PEG, isolated yields

The structures of the products were characterized employing elemental analysis, infrared (IR), ^1H and ^{13}C NMR, and mass spectrometry. For example, compound **4b** presented characteristic IR stretching frequencies in the 1670, 1610, and 1595 cm^{-1} regions for two carbonyl groups and one C=N group. The ^1H NMR spectrum of

4b exhibited two multiple signals at $\delta = (3.63\text{--}3.68)$ and $\delta = (4.40\text{--}4.56)$ for the methylene groups of the $\text{CH}_2\text{-S}$ and $\text{CH}_2\text{-N}$, respectively. A singlet appearing at $\delta = 5.76$ ppm was assigned to the methine group proton, a multiplet for $4 \text{ CH}_{\text{arom}}$ at $\delta = (7.34\text{--}7.35)$, a multiplet for CH_{arom} at $\delta = (7.63\text{--}7.69)$, a doublet of doublet for CH_{arom} at 7.85 and a doublet for CH_{arom} at $\delta = 8.13$ ppm and the N-H group was displayed at 7.58 ppm as a broad singlet. The proton decoupled ^{13}C NMR spectrum of **4b** showed 20 distinct resonances, consistent with the suggested structure.

The two-dimensional NMR spectra and **HMBC**, **HMQC**, and **COSY** correlations are useful in the signal assignment of **4b**, and various characteristic signals are shown in Fig. 2.

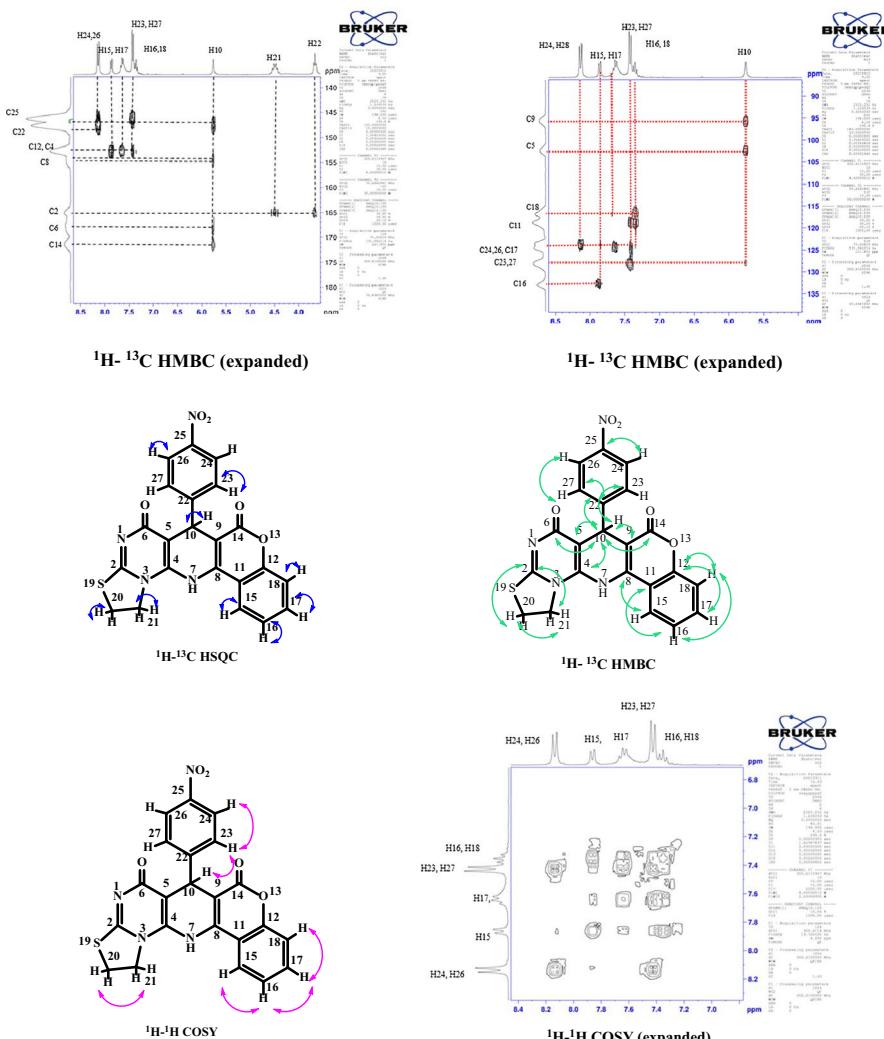


Fig. 2 COSY, HSQC, and HMBC correlations of **4b**

With the help of **HSQC** spectroscopy, all the protonated carbons could be assigned as shown in Table 3, particularly the peaks at $\delta=26.26$ ppm, assigned to the C-20 ($\text{CH}_2\text{-S}$), at $\delta=51.46$ ppm ($\text{CH}_2\text{-N}$), assigned to the C-21 methylene carbon and a singlet peak at $\delta=36.72$ ppm assigned to the C-10 assigned to the methine group proton.

Further investigation of **HMBC** supported the assignment of all the quaternary carbons and obtained ^1H - ^{13}C multi-bond correlations (two to three bonds) listed in Table 3. The structure of **4b** was elucidated by **HMBC** correlations using thiazoline ring as the starting point. In the **HMBC** spectrum, H-22 and H-21 were correlated with C-2 ($\delta=165.06$ ppm), and H10 was correlated with C-9 (2J ^1H - ^{13}C), C-5 (2J ^1H - ^{13}C), C-22 (2J ^1H - ^{13}C) appearing at 96.95, 102.44 and 146.23 ppm, respectively. In addition, the proton (H10) has three bond correlations to C-6 (3J ^1H - ^{13}C), C-23, C-27 (3J ^1H - ^{13}C), C-14 (3J ^1H - ^{13}C), C-8 (3J ^1H - ^{13}C) and C-4 (3J ^1H - ^{13}C) appearing at 166.45, 128.38, 171.45, 154.80 and 151.98 ppm, respectively.

The **HMBC** cross-peaks of the choumarine benzene ring, H-18 to C-12 (2J ^1H , $\delta=152.78$) and to C11 (3J ^1H - ^{13}C $\delta=118.68$), H-15 and H-17 to C-12 (3J ^1H , $\delta=152.78$), and H-15 to C-16 (2J ^1H , $\delta=132.73$ ppm) and H-16 to C11 (3J ^1H - ^{13}C) and C18 (3J ^1H - ^{13}C) appearing at 118.68 and 116.58 ppm, respectively. The **HMBC** cross-peaks of H-24, H-26 to C-25 (2J ^1H , $\delta=147.73$) and C-23 (2J ^1H , $\delta=124.49$) supported the assignment of all the benzene ring ^1H - ^{13}C correlations.

Based on these findings, **4b** compound was confirmed.

The proposed reaction mechanism for the synthesis of **4a** is outlined in Scheme 2. The first step is the Knoevenagel condensation reaction between the aromatic aldehyde **2** and 4-hydroxy coumarin **3** to yield the intermediate [A], which acts as Michael acceptor and would readily react with the nitrogen of 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one **1** to generate intermediate [B], which undergoes an intramolecular cyclization to afford the corresponding product **4a**.

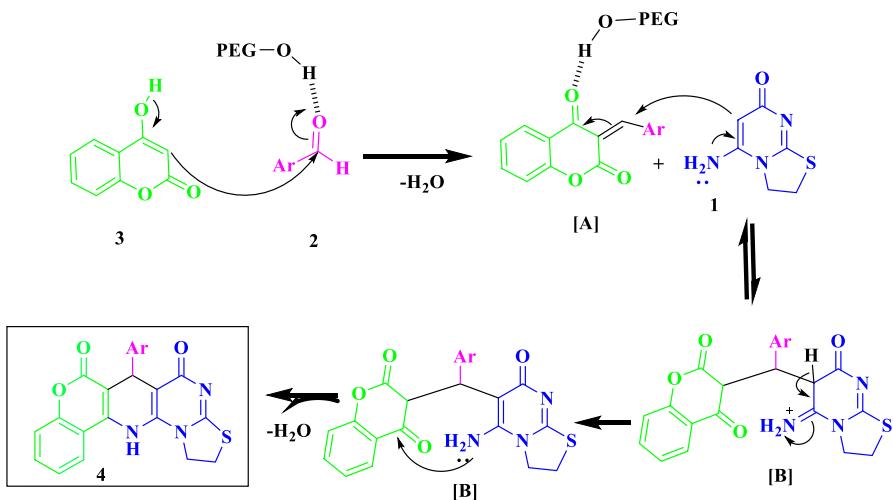
In conclusion, we successfully reported a highly efficient and environmentally friendly one-pot protocol for the reaction of fused heterocyclic enamine and various aromatic aldehydes with 4-hydroxy coumarin, resulting in the novel 6-phenyl-1,2,6,13-tetrahydro-5*H*,7*H*-chromeno[3',4':5,6]pyrido[3,2-*e*]thiazolo[3,2-*a*]pyrimidine-5,7-dione derivatives **4**. The reaction is promoted by PEG 400 as a green solvent and medium. Mild reaction conditions, slower reaction times, excellent yields (85–95%), high atom economy, and simple workup/purification are the main advantages of the present protocol.

Experimental General

All melting points reported in this work were measured on an Electrothermal 9100 apparatus. Fourier transform infrared (FT-IR) spectra were recorded using a Nicolet Avatar 370 FT-IR Therma spectrometer as KBr pellets and reported in cm^{-1} . ^1H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively, on a Bruker 300 MHz (Avance). Elemental analyses were performed on a Thermo Finnegan Flash EA 1112 series instrument. Mass spectra were obtained using Varian Mat

Table 3 Chemical shift values and their assignment to atoms for **4b**

Chemical shift H (δ in ppm)	H Atome	CAtome (ppm)	Chemical shift C (δ in ppm)	HMQC cross-peaks for a given H ppm
3.66	H20	C20	26.30	(2J ^{1}H - ^{13}C) C21 (δ =51.48 ppm), (3J ^{1}H - ^{13}C) C2 (δ =165.06 ppm)
4.50	H21	C21	51.48	C2 δ =165.06 ppm
5.76	H10	C10	36.70	(2J ^{1}H - ^{13}C) C5 (δ =102.44), (C22 δ =146.23), (C6 δ =96.95)
5.76	H10	C10	36.70	(3J ^{1}H - ^{13}C) (C6: δ =166.45), (C14: δ =171.45), (C23: δ =128.38)
7.43	H23, H27	C23, C27	128.38	(3J ^{1}H - ^{13}C) C10 δ =36.70
7.36	H18	C18	116.58	(2J ^{1}H - ^{13}C) (C12 δ =152.78), (3J ^{1}H - ^{13}C) (C11 δ =118.68)
7.65	H17	C17	132.82	(3J ^{1}H - ^{13}C) C12 δ =152.78
8.13	H24, H26	C24, C26	124.51	(2J ^{1}H - ^{13}C) C25 δ =147.73
7.86	H15	C15	123.39	(2J ^{1}H - ^{13}C) (C16 δ =132.73), (3J ^{1}H - ^{13}C) (C11 δ =118.68), (3J ^{1}H - ^{13}C) (C11 δ =118.68), (C18 δ =116.58)
7.36	H16	C16	132.73	

**Scheme 2** Plausible reaction mechanism

CH-7 at 70 eV. 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one prepared according to the previously reported literature procedure [73].

General Procedure for the Synthesis of 4

A mixture of 5-amino-2,3-dihydro-7*H*-thiazolo[3,2-*a*]pyrimidin-7-one **1** (1 mmol), aromatic aldehyde **2** (1 mmol), and 4-hydroxycoumarine **3** (1 mmol) in 0.5 mL of PEG 400 was mixed and stirred at 80 °C for 70 min. TLC monitored the progress of the reaction. After completing the reaction, the reaction mixture was allowed to return to the ambient temperature and diluted with cold water. The insoluble product (**4**) was slowly separated and washed with cold ethanol to provide the desired products (85–95% yield).

6-phenyl-2,3,6,13-tetrahydro-5*H*,7*H*-chromeno[3'4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4a)

White powder; (0.36 g, 90% yield); mp = 252–254 °C; IR(KBr) (ν_{max} /cm⁻¹): ν = 1657, 1612 (C=O), 1568 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆) δ (ppm) 3.61–3.69 (2H, m, CH₂), 4.40–4.58 (2H, m, CH₂), 5.68 (1H, s, CH), 7.14 (3H, dd, ³J_{HH} = 11.4, 7.8 Hz, ArH), 7.24–7.44 (4H, m, ArH), 7.53 (1H, m, -NH), 7.62–7.67 (1H, m, ArH), 7.85–7.90 (1H, m, ArH); ¹³C NMR (76 MHz, DMSO) δ : 26.32, 36.19, 51.45, 96.61, 102.85, 116.56, 118.63, 124.44, 124.48, 126.18, 126.90, 128.49, 132.60, 138.61, 152.95, 152.71, 154.72, 164.67, 166.68, 171.38. MS: (m/z, %), 401 (M, 2), 398 (60), 366 (12), 321 (15), 249 (45), 168 (60), 121 (45), 101 (65), 92 (28), 78 (12), 60 (10), 29 (100). Anal. Calcd. for C₂₂H₁₅N₃O₃S (401.44): C, 65.82; H, 3.77; N, 10.47%; Found: C, 65.45; H, 3.53; N, 10.06%.

6-(4-nitrophenyl)-2,3,6,13-tetrahydro-5H,7H-chromeno[3',4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4b)

Light green powder; (0.42 g, 95% yield); mp = 252–254 °C; IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): ν = 1670, 1610 (2 C=O), 1565 (C=N); ^1H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.63 (2H, dd, $^3J_{\text{HH}}=8.4$, 6.6 Hz, ArH CH₂), 4.40–4.56 (2H, m, CH₂), 5.75 (1H, s, CH), 7.43 (2H, d, $^3J_{\text{HH}}=8.7$), 7.34–7.35 (4H, m, ArH), 7.58 (1H, s, -NH), 7.63–7.69 (1H, m, ArH), 7.85 (1H, dd, $^3J_{\text{HH}}=7.8$, 1.8 Hz, ArH), 8.13 (2H, d, $^3J_{\text{HH}}=8.7$ Hz, ArH); COSY: [H-20: H-21], [H-10: H-23,27], [H-24,26: H-23,27], [H-18: H-17], [H-16: H-15], [H-16: H-17]; ^{13}C NMR, HSQC and HMBC: (76 MHz, DMSO) δ ; 26.30 (C-20, H-21), 36.70 (C-10, H-23,27), 51.48 (C-21, H-20), 95.96 (C-9), 102.44 (C-5), 116.58 (C-18), 118.68 (C-11), 123.39 (C-15), 124.49, 124.51 (C-24,26), 128.38 (C-23,27) 132.73 (C-16), 146.23 (C-22), 147.73 (C-25), 151.98 (C-4), 152.78 (C-12), 154.80 (C-8), 165.06 (C-2), 166.45 (C-6), 171.45 (C-14). MS: (m/z, %), 446 (5), 443 (22), 395 (7), 293 (63), 276 (15), 161 (60), 119 (97), 93 (95), 60 (33), 28 (100). Anal. Calcd for C₂₂H₁₄N₄O₅S (446.44): C, 59.19; H, 3.16; N, 12.55; Found: C, 59.15; H, 3.11; N, 12.26.

6-(3-nitrophenyl)-2,3,6,13-tetrahydro-5H,7H-chromeno[3',4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4c)

White powder; (0.41 g, 92% yield); mp = 255–257 °C; IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): ν = 1648, 1594 (2 C=O), 1560 (C=N); ^1H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.62–3.73 (2H, m, CH₂), 4.40–4.58 (2H, m, CH₂), 5.76 (1H, s, CH), 7.34–7.45 (2H, m, ArH), 7.55–7.72 (4H, m, ArH), 7.85 (1H, dd, $^3J_{\text{HH}}=7.5$, 1.5 Hz ArH), 7.92 (1H, s, -NH), 8.08 (1H, d, $^3J_{\text{HH}}=8.1$ Hz, ArH); ^{13}C NMR (76 MHz, DMSO) δ ; 26.25, 36.23, 51.48, 95.83, 102.33, 116.60, 118.69, 121.49, 124.51, 124.55, 130.01, 132.76, 134.14, 141.68, 148.36, 152.52, 152.79, 154.92, 165.07, 166.48, 171.42. MS: (m/z, %), 446 (5), 294 (25), 276 (75), 247 (54), 167 (32), 121 (85), 92 (100), 64 (35), 29 (100). Anal. Calcd for C₂₂H₁₄N₄O₅S (446.44): C, 59.19; H, 3.16; N, 12.55%; Found: C, 59.05; H, 3.11; N, 12.36%.

6-(2-chlorophenyl)-2,3,6,13-tetrahydro-5H,7H-chromeno[3',4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4d)

White powder; (0.41 g, 94% yield); mp = 242–244 °C; IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): ν = 1654, 1578 (2C=O), 1531 (C=N); ^1H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.59–3.71 (2H, m, CH₂), 4.39–4.59 (2H, m, CH₂), 5.64 (1H, s, CH), 7.21–7.30 (2H, m, ArH), 7.33–7.46 (5H, m, -NH, ArH), 7.59–7.65 (1H, m, ArH), 7.89 (1H, dd, $^3J_{\text{HH}}=7.8$, 1.5 Hz, ArH); ^{13}C NMR (76 MHz, DMSO) δ ; 26.17, 35.91, 51.43, 96.44, 102.23, 116.46, 118.76, 124.42, 124.52, 126.98, 128.41, 130.32, 130.39, 132.53, 133.03, 136.99, 152.08, 152.58, 154.33, 164.27, 166.01, 171.36. MS: (m/z, %), 435 (M, 10), 432 (72), 321 (8), 282 (100), 254 (55), 168 (100), 120 (72), 91 (95), 59 (70), 28 (90). Anal. Calcd for C₂₂H₁₄ClN₃O₃S (435.88): C, 60.62; H, 3.24; N, 9.64%; Found: C, 60.55; H, 3.11; N, 9.46%.

6-(3,4-dichlorophenyl)-2,3,6,13-tetrahydro-5H,7H-chromeno[3'4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4e)

White powder; (0.43 g, 92% yield); mp = 244–246 °C; IR (KBr) (ν_{max} /cm⁻¹): ν = 1658, 1613 (2C=O), 1568 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.61–3.70 (2H, m, CH₂), 4.39–4.55 (2H, m, CH₂), 5.65 (1H, s, CH), 7.11–7.15 (1H, m, ArH), 7.31–7.42 (3H, m, ArH), 7.48 (1H, d, 8.7 Hz, ArH), 7.55 (1H, s, -NH), 7.60–7.66 (1H, m, ArH), 7.85 (1H, dd, ³J_{HH} = 7.8, 1.5 Hz, ArH); ¹³C NMR (76 MHz, DMSO) δ : 26.28, 35.82, 51.45, 96.01, 102.33, 116.55, 118.70, 124.45, 124.49, 127.64, 128.76, 129.02, 130.48, 131.17, 132.66, 140.49, 152.77, 153.24, 154.83, 164.96, 166.48, 171.40. MS: (m/z, %), 473 (M⁺, 10), 470 (17), 381 (38), 316 (100), 276 (72), 252 (33), 197 (51), 161 (70), 146 (68), 119 (85), 91 (85), 76 (27), 64 (70), 43 (35), 29 (70). Anal. Calcd for C₂₂H₁₃C₁₂N₃O₃S (470.32): C, 56.18; H, 2.79; N, 8.93%; Found: C, 56.15; H, 2.51; N, 8.76.

6-(4-chlorophenyl)-2,3,6,13-tetrahydro-5H,7H-chromeno[3'4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4f)

White powder; (0.39 g, 90% yield); mp = 245–247 °C; IR(KBr) (ν_{max} /cm⁻¹): ν = 1657, 1612 (2C=O), 1568 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.61–3.67 (2H, m, CH₂), 4.39–4.56 (2H, m, CH₂), 5.63 (1H, s, CH), 7.14–7.18 (2H, m, ArH), 7.20–7.33 (4H, m, ArH), 7.52 (1H, s, -NH), 7.61–7.70 (1H, m, ArH), 7.86 (1H, dd, ³J_{HH} = 8.1, 1.5 Hz, ArH); ¹³C NMR (76 MHz, DMSO) δ : 26.27, 35.87, 51.42, 96.40, 102.68, 116.54, 118.69, 124.47, 124.48, 128.35, 128.92, 130.76, 132.62, 137.89, 152.71, 152.73, 154.73, 164.75, 166.64, 171.51. MS: (m/z, %), 435(M, 5), 432 (50), 283 (58), 254 (10), 168 (15), 121(20), 28 (100). Anal. Calcd for C₂₂H₁₄ClN₃O₃S (435.04): C, 60.62; H, 3.24; N, 9.64%; Found: C, 60.55; H, 3.11; N, 9.46%.

6-(3-bromophenyl)-2,3,6,13-tetrahydro-5H,7H-chromeno[3'4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4 g)

White powder; (0.43 g, 89% yield); mp = 242–244 °C; IR (KBr) (ν_{max} /cm⁻¹): ν = 1664, 1612 (2 C=O), 1565 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.58–3.68 (2H, m, CH₂), 4.39–4.56 (2H, m, CH₂), 5.67 (1H, s, CH), 7.17–7.35 (3H, m, ArH), 7.36–7.44 (3H, m, ArH), 7.54 (1H, s, -NH), 7.61–7.67 (1H, m, ArH), 7.86 (1H, dd, ³J_{HH} = 7.8, 1.8 Hz, ArH); ¹³C NMR (76 MHz, DMSO) δ : 26.28, 36.07, 51.46, 96.15, 116.57, 118.67, 122.08, 124.48, 124.62, 126.19, 129.17, 129.58, 130.61, 132.66, 141.92, 152.74, 152.98, 154.79, 164.87, 166.52, 171.37. MS: (m/z, %), 480 (24), 477 (42), 327 (100), 248 (83), 168 (95), 146(94), 120 (100), 92 (90), 65 (38), 29 (100). Anal. Calcd for C₂₂H₁₄BrN₃O₃S (480.34): C, 55.01; H, 2.94; N, 8.75%; Found: C, 55.15; H, 2.81; N, 8.66%.

6-(3-hydroxyphenyl)-2,3,6,13-tetrahydro-5H,7H-chromeno[3'4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4 h)

White powder; (0.35 g, 85% yield); mp = 241–243 °C; IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): ν = 1649, 1607 (2 C=O), 1573 (C=N); ^1H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.61–3.71 (2H, m, CH₂), 4.38–4.58 (2H, m, CH₂), 5.56 (1H, s, CH), 6.56–6.59 (3H, m, ArH), 7.02–7.07 (1H, m, ArH), 7.34–7.41 (2H, m, ArH), 7.44 (1H, s, -NH), 7.61–7.69 (1H, m, ArH), 7.87–7.92 (1H, m, ArH), 9.17 (1H, s, -OH); ^{13}C NMR (76 MHz, DMSO) δ : 26.23, 36.13, 51.39, 96.76, 102.84, 113.18, 113.86, 116.53, 117.57, 118.68, 124.48, 124.50, 129.36, 132.59, 140.22, 152.63, 152.66, 154.61, 157.70, 164.50, 166.83, 171.65. MS: (m/z, %), 267 (80), 265 (100), 248 (20), 169 (90), 147 (45), 121 (100), 92 (35), 77 (15), 59 (38), 29 (100). Anal. Calcd for C₂₂H₁₅N₃O₄S (417.44): C, 63.30; H, 3.62; N, 10.07%. Found: C, 63.45; H, 3.51; N, 10.02%.

6-(3,4-dihydroxyphenyl)-2,3,6,13-tetrahydro-5H,7H-chromeno[3'4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4i)

White powder; (0.33 g, 95% yield); mp = 244–246 °C; IR(KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): ν = 1669, 1612 (2 C=O), 1568 (C=N); ^1H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.59–3.68 (2H, m, CH₂), 4.41–4.56 (2H, m, CH₂), 5.50 (1H, s, CH), 6.38 (1H, d, $^3J_{\text{HH}}=7.5$ Hz, ArH), 6.56 (1H, d, $^3J_{\text{HH}}=2.4$ Hz, ArH), 6.61 (1H, d, $^3J_{\text{HH}}=8.4$ Hz, ArH), 7.33–7.43 (2H, m, ArH), 7.49 (1H, s, -NH), 7.61 (1H, t, $^3J_{\text{HH}}=7.5$ Hz, ArH), 7.87 (1H, d, $^3J_{\text{HH}}=16.2$ Hz, ArH), 8.62 (1H, s, -OH), 8.68 (1H, s, -OH); ^{13}C NMR (76 MHz, DMSO) δ : 26.23, 35.50, 51.37, 97.03, 103.18, 114.47, 115.72, 116.51, 117.57, 118.73, 124.45, 124.47, 129.23, 132.51, 143.65, 145.31, 152.35, 152.63, 154.52, 164.30, 166.92, 171.64. MS: (m/z, %), 319 (17), 262 (5), 233 (5), 167 (58), 119 (48), 109 (100), 102 (55), 80 (35), 63 (37), 28 (93); Anal. Calcd for C₂₂H₁₅N₃O₅S (433.44): C, 60.96; H, 3.49; N, 9.69%; Found: C, 60.75; H, 3.41; N, 9.56%.

6-(5-bromo-2-hydroxyphenyl)-2,3,6,13-tetrahydro-5H,7H-chromeno[3'4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4j)

Ligh green powder; (0.42 g, 85% yield); mp = 238–240 °C; IR (KBr) ($\nu_{\text{max}}/\text{cm}^{-1}$): ν = 1669, 1612 (2 C=O), 1566 (C=N); ^1H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.61–3.71 (2H, m, CH₂), 4.38–4.56 (2H, m, CH₂), 5.57 (1H, s, CH), 6.65 (1H, t, $^3J_{\text{HH}}=4.8$ Hz, ArH), 7.13–7.21 (2H, m, ArH), 7.33–7.47 (3H, m, -NH, ArH), 7.60 (1H, t, $^3J_{\text{HH}}=7.8$ Hz, ArH), 7.87 (1H, d, $^3J_{\text{HH}}=7.8$ Hz, ArH), 9.62 (1H, s, OH); ^{13}C NMR (76 MHz, DMSO) δ : 26.12, 33.00, 51.38, 96.62, 103.23, 109.98, 116.42, 117.43, 118.79, 124.38, 124.42, 128.12, 130.11, 131.56, 132.34, 152.19 152.48, 154.06, 155.57, 166.16, 166.87, 171.54. MS: (m/z, %), 334 (10), 328 (80), 297 (10), 246 (9), 186 (57), 171 (88), 161 (68), 121 (92), 92 (90), 65 (90), 39 (85), 29 (100);

Anal. Calcd for $C_{22}H_{14}BrN_3O_4S$ (496.34) C, 53.24; H, 2.84; N, 8.47. Found: C, 53.35; H, 2.71; N, 8.56.

6-(4-isopropylphenyl)-2,3,6,13-tetrahydro-5*H*,7*H*-chromeno[3',4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4 k)

White powder; (0.38 g, 85% yield); mp=278–280 °C; IR (KBr) (ν_{max} /cm⁻¹): ν =1654, 1578 (2 C=O), 1531 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 1.18–1.20 (6H, d, ³J_{HH}=6.9, 2 CH₃), 2.80–2.89 (1H, m, CH), 3.61–3.71 (2H, m, CH₂), 4.39–4.58 (2H, m, CH₂), 5.61 (1H, s, CH), 7.03 (4H, dd, ³J_{HH}=8.1, 2.4 Hz, ArH), 7.33–7.43 (2H, m, ArH), 7.45 (1H, s, -NH), 7.61–7.67 (1H, m, ArH), 7.86 (1H, dd, ³J_{HH}=7.8, 1.5 Hz, ArH); ¹³C NMR (76 MHz, DMSO) δ; 24.39, 24.41, 26.23, 33.39, 35.89, 51.39, 96.78, 102.93, 116.53, 118.71, 124.43, 124.59, 126.38, 126.79, 132.53, 135.91, 145.53, 146.03, 152.35, 152.70, 154.64, 164.53, 166.80, 171.64. MS: (m/z, %), 443 (M, 5), 442 (15), 425 (10), 292 (98), 276 (45), 249 (100), 161 (67), 120 (98), 92 (90), 60 (30), 43 (38), 28 (98);. Anal. Calcd for $C_{25}H_{21}N_3O_3S$ (443.52): C, 67.70; H, 4.77; N, 9.47%; Found: C, 67.65; H, 4.57; N, 9.66%.

6-(4-(dimethylamino)phenyl)-2,3,6,13-tetrahydro-5*H*,7*H*-chromeno[3',4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4 l)

White powder; (0.42 g, 95% yield); mp=218–220 °C; IR (KBr) (ν_{max} /cm⁻¹): ν =1661, 1610 (2 C=O), 1566 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 2.85(6H, s, 2CH₃), 3.59–3.68 (2H, m, CH₂), 4.38–4.54 (2H, m, CH₂), 5.64 (1H, s, CH), 6.62–6.66 (2H, m, ArH), 6.91 (2H, d, ³J_{HH}=8.4, Hz, ArH), 7.33–7.41 (2H, m, ArH), 7.43 (1H, s, -NH), 7.61–7.67 (1H, m, ArH), 7.85 (1H, dd, ³J_{HH}=7.8, 1.8 Hz, ArH); ¹³C NMR (76 MHz, DMSO) δ; 26.21, 35.29, 40.83, 51.35, 97.08, 103.22, 112.88, 116.52, 118.75, 124.39, 124.43, 125.98, 127.76, 132.46, 149.12, 152.28, 152.66, 154.55, 164.27, 166.97, 171.62. MS: (m/z, %), 414 (5), 370 (28), 319 (50), 295 (78), 251 (80), 175 (80), 133 (77), 120 (85), 77 (78), 65 (63), 43 (60), 29 (100); Anal. Calcd for $C_{24}H_{20}N_4O_3S$ (444.51): C, 64.85; H, 4.54; N, 12.60%; Found: C, 64.75; H, 4.41; N, 12.46.%.

6-(4-methoxyphenyl)-2,3,6,13-tetrahydro-5*H*,7*H*-chromeno[3',4':5,6]pyrido[3,2-e]isothiazolo[2,3-a]pyrimidine-5,7-dione (4 m)

White powder; (0.40 g, 92% yield); mp=223–225 °C; IR(KBr) (ν_{max} /cm⁻¹): ν =1665, 1612 (2C=O), 1565 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.61–3.68 (2H, m, CH₂), 3.73 (3H, s, OCH₃), 4.39–4.58 (2H, m, CH₂), 5.59 (1H, s, CH), 6.76–6.83 (2H, m, ArH), 7.02–7.05 (2H, d, ³J_{HH}=8.4 Hz ArH), 7.32–7.43 (2H, m, ArH), 7.47 (1H, s, -NH), 7.60–7.67 (1H, m, ArH), 7.86 (1H, dd, ³J_{HH}=8.1, 1.8 Hz, ArH); ¹³C NMR (76 MHz, DMSO) δ; 26.24, 35.50, 51.39, 55.44, 96.92,

103.07, 113.86, 116.52, 118.74, 124.42, 124.46, 130.24, 132.51, 152.56, 152.69, 154.62, 157.82, 164.46, 166.82, 171.61. MS: (m/z, %), 282 (22), 279 (92), 251(75), 251 (75), 161 (77), 133 (78), 108 (85), 92 (78), 65 (80), 60 (100), 29 (75); Anal. Calcd for $C_{23}H_{17}N_3O_4S$ (431.47): C, 64.03; H, 3.97; N, 9.74%; Found: C, 63.95; H, 3.81; N, 9.56%.

6-(2,4-dimethoxyphenyl)-2,3,6,13-tetrahydro-5*H*,7*H*-chromeno[3',4':5,6]pyrido[3,2-*e*]isothiazolo[2,3-*a*]pyrimidine-5,7-dione (4n)

White powder; (0.41 g, 95% yield); mp = 218–220 °C; IR (KBr) (ν_{max} /cm^{−1}): ν = 1660, 1612 (2 C=O), 1565 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.59 (3H, s, CH₃), 3.61–3.68 (2H, m, CH₂), 3.74 (3H, s, CH₃), 4.39–4.58 (2H, m, CH₂), 5.57 (1H, s, CH), 6.42–6.50 (2H, m, ArH), 7.08 (1H, d, ³J_{HH} = 8.4, ArH), 7.31–7.40 (3H, m, -NH, ArH), 7.57–7.63 (1H, m, ArH), 7.87 (1H, dd, ³J_{HH} = 7.8, 1.8 Hz ArH); ¹³C NMR (76 MHz, DMSO) δ : 26.14, 32.41, 51.34, 55.53, 56.17, 97.68, 99.20, 103.53, 104.37, 116.38, 118.88, 119.24, 124.34, 124.37, 129.37, 132.23, 152.20, 152.46, 153.92, 158.53, 159.48, 163.55, 166.36, 171.53. MS: (m/z, %), 428 (5), 320 (15), 312 (20), 309 (43), 282 (95), 225 (24), 198 (22), 161 (38), 137 (95), 119 (43), 91 (35), 63 (15), 29 (100); Anal. Calcd for $C_{24}H_{19}N_3O_5S$ (461.10): C, 62.46; H, 4.15; N, 9.11%; Found: C, 62.65; H, 4.11; N, 9.06%.

4-(5,7-dioxo-3,5,7,13-tetrahydro-2*H*,6*H*-chromeno[3',4':5,6]pyrido[3,2-*e*]isothiazolo[2,3-*a*]pyrimidin-6-yl)benzonitrile (4o)

White powder; (0.39 g, 91% yield); mp = 256–258 °C; IR(KBr) (ν_{max} /cm^{−1}): ν = 2223 (C≡N), 1678, 1619 (2 C=O), 1569 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.56–3.71 (2H, m, CH₂), 4.38–4.56 (2H, m, CH₂), 5.71 (1H, s, CH), 7.32–7.43 (4H, m, ArH), 7.57 (1H, m, -NH), 7.61–7.67 (1H, m, ArH), 7.69–7.87 (2H, m, ArH), 7.82–7.90 (2H, m, ArH); ¹³C NMR (76 MHz, DMSO) δ : 26.29, 36.69, 51.45, 95.99, 102.26, 109.01, 116.56, 118.67, 119.58, 124.47, 124.49, 128.17, 132.40, 132.69, 145.36, 152.58, 152.77, 154.82, 164.99, 166.51, 171.49. MS: (m/z, %), m/z: 426 (M, 10), 423 (55), 393 (32), 321 (40), 274 (100), 246 (70), 202 (55), 168 (75), 146 (80), 121(100), 77 (68), 60 (85), 41 (83), 29 (85); Anal. Calcd for $C_{23}H_{14}N_4O_3S$ (426.08): C, 64.78; H, 3.31; N, 13.14%; Found: C, 64.71; H, 3.22; N, 13.06%.

6-(naphthalen-2-yl)-2,3,6,13-tetrahydro-5*H*,7*H*-chromeno[3',4':5,6]pyrido[3,2-*e*]isothiazolo[2,3-*a*]pyrimidine-5,7-dione (4p)

Cream powder; (0.38 g, 85% yield); mp = 249–251 °C; IR (KBr) (ν_{max} /cm^{−1}): ν = 1654, 1578 (2 C=O), 1531 (C=N); ¹H NMR (300.13 MHz, DMSO-d₆): δ (ppm) 3.63–3.70 (2H, m, CH₂), 4.41–4.59 (2H, m, CH₂), 5.83 (1H, s, CH), 7.32–7.37 (2H, m, ArH), 7.40–7.46 (3H, m, ArH), 7.52 (1H, s, -NH), 7.63–7.71 (2H, m, ArH),

7.77- 7.82 (2H, m, ArH), 7.85- 7.91(2H, m, ArH); ^{13}C NMR (76 MHz, DMSO) δ ; 26.25, 36.51, 51.43, 96.72, 103.00, 116.57, 118.82, 124.49, 124.54, 124.88, 125.76, 126.04, 126.29, 127.68, 127.93, 128.06, 132.09, 132.59, 133.48, 136.47, 152.78, 152.80, 154.75, 164.64, 166.76, 171.78. MS: (m/z, %), 451 (M, 5), 448 (18), 301 (33), 270 (2), 244 (5), 216 (3), 176 (8), 140 (10), 120 (12), 43 (5), 28 (100); Anal. Calcd for $\text{C}_{26}\text{H}_{17}\text{N}_3\text{O}_3\text{S}$ (451.50): C, 69.17; H, 3.80; N, 9.31%; Found: C, 69.15; H, 3.71; N, 9.26%.

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Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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