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Efficient synthesis of novel chromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine derivatives via three-component reaction using acidic ionic liquid catalysts in ethylene glycol

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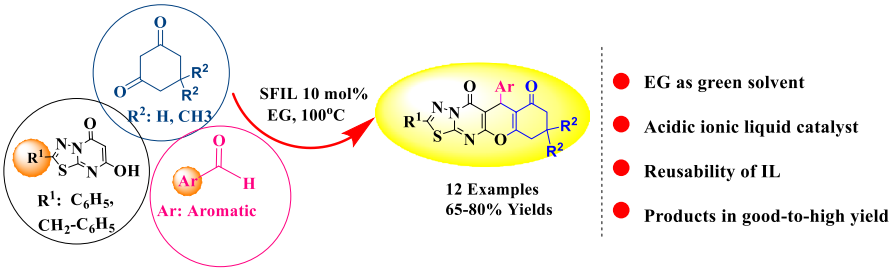
Abstract

A facile and efficient greener synthesis of a novel four-fused ring heterocyclic system via three-component reactions of [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one, aromatic aldehyde, and 1,3-cyclohexanediones, in the presence of 1-(4-sulfonic acid) butyl-3-methylimidazolium hydrogen sulfate, has been presented. The synthesized compounds were characterized by mass spectrometry, IR, ^{1}H-NMR, ^{13}C-NMR, and elemental analysis. The remarkable features of this method are using acidic ionic liquid catalyst, green solvent media, short reaction time, good yields, and simple purification techniques.

Graphical abstract



Keywords Green chemistry · Three-component reactions · Sulfonic acid-functionalized ionic liquids · Chromenopyrimidine · 1,3,4-thiadiazolopyrimidine

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Introduction

Heterocycles with molecular hybrids comprising N, O, and S in their framework as the most common heteroatoms are considered one of the vital classes of organic compounds [1]. Nitrogen-based heterocycles are known as biologically active species. They are found in a lot of naturally occurring compounds and numerous biologically active products [2]. Among these, thiadiazoles represent an important class of heterocyclic structural motifs [3]. They inhibit bacterial and cancer cell proliferation by disrupting the DNA replication process and are known as the main structure of antitumor agents, possibly due to the presence of toxophoric N–C–S moiety [4, 5]. 1,3,4-Thiadiazolo[3,2-*a*]pyrimidines induced a wide range of biological activities such as antiglycation agents [6], anticancer [7], antioxidant [8], antimicrobial [9, 10], antitumor [11], and analgesic activities [12] (Fig. 1, A and B).

4*H*-Chromenes [13] are important oxygen-containing compounds that are found in natural compounds such as antibiotics, alkaloids, and iridoids [14]. Also, these compounds, with their biological and medicinal activities such as cytotoxic activity [15], anticancer [16], antifungal [17], antimicrobial [18], mutagenicity [19], and antibacterial [20], have attracted a lot of attention. Some drugs containing a 4*H*-chromene derivative are presented in Fig. 1, C-E [21–24]. In addition, they are of particular importance in the treatment of neurological diseases including Parkinson's disease [25], Alzheimer's disease [26], and Down's syndrome [27].

Ionic liquids (IL) are low melting point salts and play an important role in the development of an eco-friendly, sustainable procedure for the synthesis of heterocyclic compounds. The ideal properties of IL are very low toxicity, very low vapor pressure,

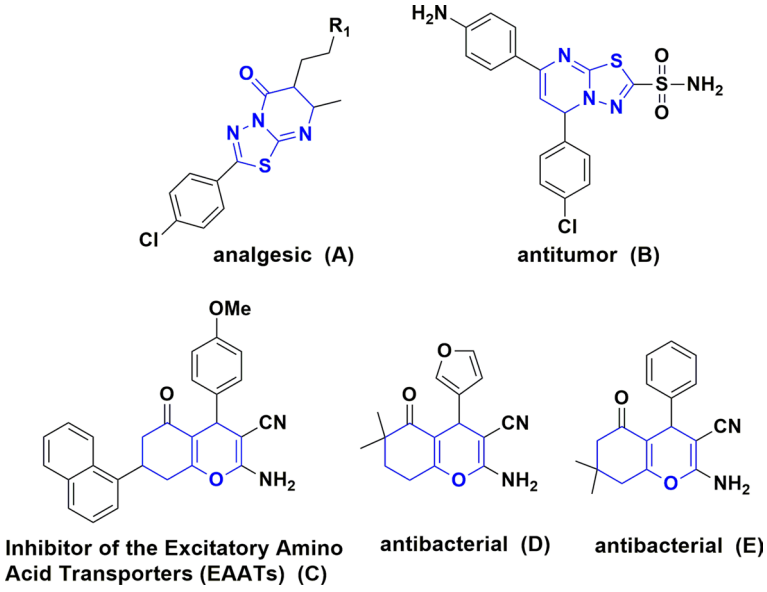
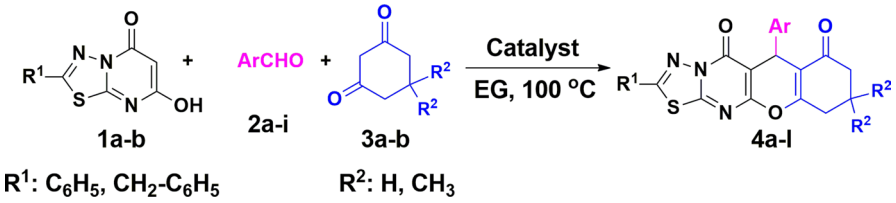


Fig. 1 Biologically active thiadiazolopyrimidine and chromenopyrimidine



Scheme 1 Synthesis of new chromeno[2,3-*d*]thiadiazolo[3,2-*a*]pyrimidine derivatives

nonflammability, high catalytic activity, good compatibility with organic compounds, and also reusability [28–33]. IL can be used as reaction mediums and catalysts [34]. The Brönsted acidic ionic liquids (BAILs) group introduced as a SO_3H-functionalized ionic liquids have unique physicochemical properties and also gaining increasing attention in synthetic organic chemistry because they are environmentally benign, nontoxic, and easily recoverable [35–37]. In this direction, the synthesis of the 1-butyl-3-methyl imidazolium (Bmim) cation with an acid sulfonic group, to obtain 1-(4-sulfonic acid)-butyl-3-methyl imidazolium, with bisulfate counterion [HSO_4^-], was examined [38, 39]. Due to their unique properties, these compounds are widely used in various fields of study such as engineering, biochemistry, and physics [40].

Multicomponent reactions are a good alternative to multistep and time-consuming synthesis. These reactions lead to the rapid synthesis of complex products with high atom economy and selectivity. As a result, less waste and fewer unwanted by-products are expected during the reaction. MCRs also meet the green and efficient synthesis concepts by saving on reagents and solvents, displaying shorter reaction times, and access to the reduction of cost, energy, waste, and unwanted by-products [41–50].

Considering the abovementioned biological properties, we assumed the importance of compounds containing both 4*H*-chromane and 1,3,4-thiadiazlo[3,2-*a*]pyrimidine-5-ones possess interesting pharmacological properties. In continuation of our successful previous synthetic protocol for the synthesis of heterocyclic compounds [51–53], the development of novel polycyclic heterocyclic compounds through reactions of [1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one **1**, aromatic aldehydes **2**, and 1,3-cyclohexanedione **3** in the presence of ionic liquid (SFIL) (1-(4-sulfonic acid) butyl-3-methyl-imidazolium hydrogen sulfate) leads to 4*H*-chromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*] pyrimidine (Scheme 1).

It is probable that the new fused heterocyclic system will exhibit properties of both components; finally, we have designed and synthesized their derivatives. To the best of our knowledge, there is no report for the synthesis of 4*H*-chromeno[2,3-*d*][1,3,4] thiadiazolo[3,2-*a*]pyrimidine as heterocyclic hybrids.

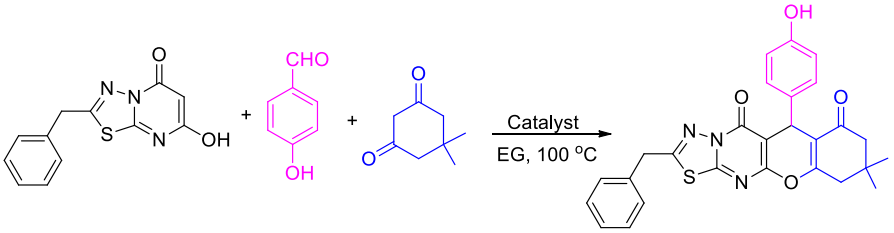
Results and discussion

A model reaction with 2-benzyl-7-hydroxy-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one (**1**), 4-hydroxybenzaldehyde (**2c**), and dimedone (**3**) was screened with various catalysts (Table 1). When the reaction was carried out without a catalyst

at 100 °C for 24 h in ethylene glycol (EG) as solvent using equimolar amounts of all three substates, the desired product **4c** was obtained in a trace amount (Table 1, entry 1).

This indicates that there is scope to use a catalyst for this condensation reaction. Using 10 mol% of *N*,*N*-diisopropylethylamine; 10 mol% of triethylamine as basic catalysts, and 10 mol% of lactic acid; trifluoroacetic acid and $TiCl_3$, $ZnCl_2$ as Lewis acid, the model reaction was applied at 100 °C in ethylene glycol (0.5 ml), leading to moderate yields of product **4c** (Table 1, entries 2–7). Next, ionic liquids such as $[Et_3NH]$ $[HSO_4]$, [bmim]Br, benzyltriethylammonium chloride, $[bmim]BF_4$, [bmim]

Table 1 Optimization of the reaction conditions



Yield (%)	Time (h)	Catalyst (10 mol%)	Entry
trace	24	No	1
30	12	DIPEA[a]	2
30	12	Et_3N	3
50	12	Lactic acid	4
55	12	Trifluoroacetic acid	5
45	12	$TiCl_3$	6
40	12	$ZnCl_2$	7
40	12	$[Et_3NH][HSO_4]$[b]	8
70	6	PTC[c]	9
60	6	[bmim]Br[d]	10
50	6	$[bmim]BF_4$[e]	11
50	6	$[bmim]PF_6$[f]	12
75	3	SFIL[g]	13

Reaction conditions: 2-benzyl-7-hydroxy-[1,3,4]thiadiazolo[3,2-α]pyrimidin-5-one (1 mmol), 4-hydroxybenzaldehyde (1 mmol), dimedone (1 mmol), 4-hydroxybenzaldehyde (1 mmol), at 100 °C in ethylene glycol (0.5 ml)

[a]*N*,*N*-diisopropylethylamine

[b]Triethylammonium hydrogen sulfate

[c]Benzyltriethylammonium chloride

[d]1-butyl-3-methylimidazolium bromide

[e]1-butyl-3-methylimidazolium tetrafluoroborate

[f]1-butyl-3-methyl imidazolium hexafluorophosphate

[g]1-(4-sulfonic acid)butyl-3-methylimidazolium hydrogen sulfate

PF_6, and SFIL have examined their promotion in the reaction (Table 1, entries 8–13). Experimental data have exhibited that SFIL ionic liquid compared to other catalysts, provided the best result, with a 75% yield (Table 1, entry 13). Then, the effects of various solvents, such as H_2O, EtOH, H_2O/EtOH (1:1), CH_3CN, DMF, glycerol, PEG 400, and solvent-free medium by using a catalytic amount of SFIL (Table 2, entries 1–8), were eminent that EG is the best solvent for the desired transmutation due to fast reaction rate and high yield (Table 2, entry 9). To optimize catalyst loading, 5 mol%, 10 mol%, and 20 mol% were monitored in model reaction, respectively; in 5 mol% of the catalyst, the reaction was not complete (Table 2, entry 12), and 10 mol% of the catalyst was optimum loading for completing the reaction with 75% yield (Table 2, entry 11); further loading of catalyst to 20 mol% did not significantly affect the reaction yield (Table 2, entries [12,13]). Finally, the effect of temperature was examined for the model reaction in EG. The best result was obtained at 100 °C with a 75% yield (Table 2, entries 11). Using 110 °C as a heating temperature did not result in further improvement of the reaction outcome.

Overall, the screening discloses that the reaction in EG as a green solvent in the presence of 10 mol% SFIL as the SO_3H-functionalised ionic liquid at 100 °C gave the best result (Table 2, entry 11). Subsequently, the domain and generality of the procedure were also checked for the synthesis of various chromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine derivatives under optimized reaction conditions (Table 3). Under optimal conditions, the domain of reaction was evaluated with aldehydes and two heterocyclics 1,3-dions **1**. We observed that aromatic aldehydes bearing electron-donating groups, such as 4-methyl, 4-methoxy, 4-hydroxy, and benzaldehyde, gave the desired products in good to high yield, while aromatic aldehydes containing the electron-withdrawing substituents such as 4-cyano, 4-nitro,

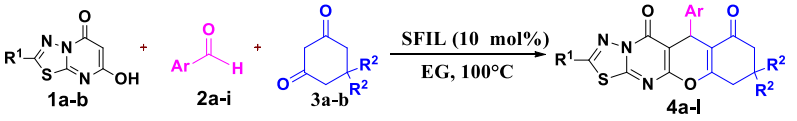
Table 2 Optimization of solvent

Entry	Solvent	Catalyst loading (mol%)	Temperature (°C)	Time (h)	Yield (%)
1	H_2O	SFIL (10)	Reflux	12	30
2	EtOH	SFIL (10)	Reflux	12	15
3	H_2O/EtOH (1:1)	SFIL (10)	Reflux	12	20
4	CH_3CN	SFIL (10)	Reflux	12	50
5	DMF	SFIL (10)	110	12	15
6	Glycerol	SFIL (10)	110	5	60
7	PEG 400	SFIL (10)	110	12	60
8	No	SFIL (10)	110	12	60
9	EG	SFIL (10)	110	3	75
10	EG	SFIL (10)	90	5	60
11	EG	SFIL (10)	100	3	75
12	EG	SFIL (5)	100	3	60
13	EG	SFIL (20)	100	3	75

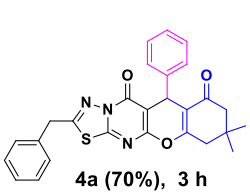
Reaction conditions: 2-benzyl-7-hydroxy-[1,3,4]thiadiazolo[3,2-a]pyrimidin-5-one (1 mmol), 4-hydroxybenzaldehyde (1 mmol), dimedone (1 mmol(

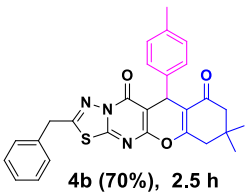
and 4-chloro were investigated, but unluckily, trace amounts of the product were formed. Thiophene-2-carbaldehyde as a heterocyclic aldehyde reacted efficiently to generate the desired product in excellent yields. However, no product was produced when other heteroaromatic aldehydes, including pyridine-3-carbaldehyde, pyridine-2-carbaldehyde, and furfural under the optimized condition. Also, when we tested aliphatic aldehydes (cinnamaldehyde, capraldehyde, and glutaraldehyde) in the optimized reaction, no desired product was obtained.

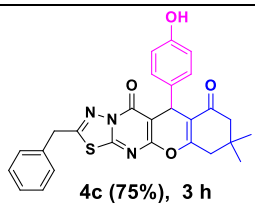
Table 3 Synthesis of new chromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine derivatives

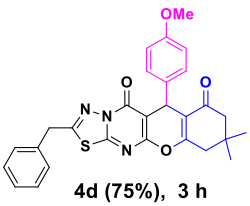


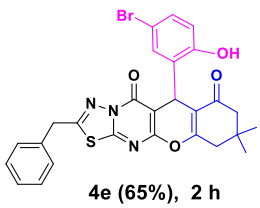
1a-b + 2a-i + 3a-b → 4a-l

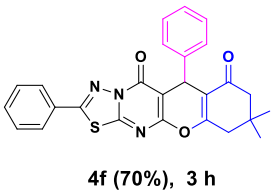

4a (70%), 3 h

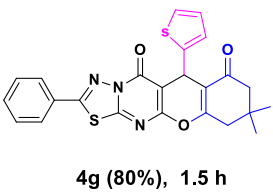

4b (70%), 2.5 h

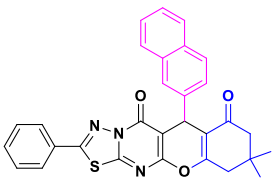

4c (75%), 3 h

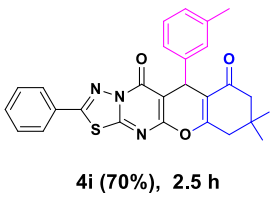

4d (75%), 3 h

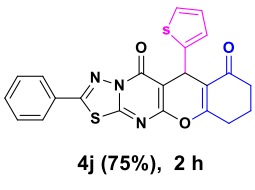

4e (65%), 2 h

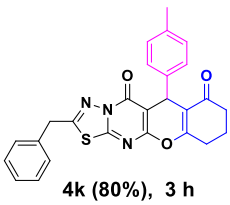

4f (70%), 3 h

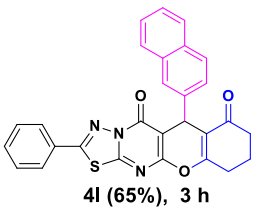

4g (80%), 1.5 h

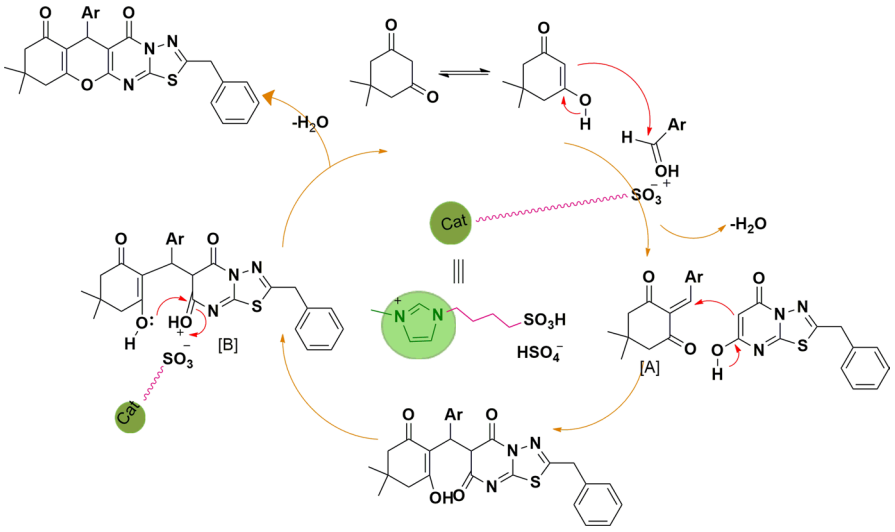

4h (78%), 2 h


4i (70%), 2.5 h


4j (75%), 2 h


4k (80%), 3 h


4l (65%), 3 h



Scheme 2 The plausible mechanism for the synthesis of product **4**

From economic and environmental viewpoints, the possibility of recycling catalysts is an important subject in the present reaction. After completion, the reaction was eluted with MeOH: H_2O (2:1) and filtered to obtain the solid residue. To recycle SFIL, the filtrated solvents evaporated under a vacuum and the remainder was eluted with n-hexane (3 × 1 mL), dried within 2 h at 50 °C, and used again. This regenerated catalyst has been used for at least four cycles without considerably losing its catalytic activity.

All final products (**4a–l**) were characterized by their IR, ^{1}H NMR, and ^{13}C NMR spectra, mass spectrometric, and elemental analyses (see Supplementary data). The mass spectrum for **4a** revealed the expected molecular ion peak at $m/z = 469$.

The assumed mechanism for the synthesis of 2-benzyl-7,7-dimethyl-10-phenyl-7,8-dihydrochromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione is proposed in Scheme 2. Based on the reported literature [54], the carbonyl group of aldehyde was activated by the SFIL catalyst to promote Knoevenagel condensation. The protonated carbonyl group of aldehyde was attacked by the enolic form of dimedone to form intermediate [**A**], followed by Michael's addition reaction that took place with 2-benzyl-7-hydroxy-5*H*-[1,3,4]thiadiazolo[3,2-*a*]pyrimidin-5-one **1** affording intermediate [**B**] which undergoes an intramolecular cyclization, leading to product **4a**.

Conclusion

In summary, the four-cyclic 4*H*-chromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidines prepared in this work could be important scaffolds for biological activities. We have introduced a green and facile method for the synthesis of chromeno[2,3-*d*]

[1,3,4]thiadiazolo[3,2-*a*]pyrimidine core through the one-pot, the three-component reaction between dimedone, substituted benzaldehyde, and [1,3,4]thiadiazolo[3,2-*a*] pyrimidin-5-one in the presence of SFIL as a biocompatible ionic liquid catalyst in EG as green solvent, and temperate condition with good to high yield. The advantages of this research are the operational simplicity, reusability of the IL, short reaction time, availability of raw materials, and easy purification.

Experimental general

All reported melting points were performed by Electrothermal 9100 apparatus and are uncorrected. IR spectra (KBr disks) were recorded on a Nicolet Avatar 370 FTIR Therma instrument. ^{1}H and ^{13}C NMR spectra were verified on a Bruker DPX-300 Avance spectrometer at 300.13 and 75.47 MHz, respectively. The mass spectra were performed by a Varian Mat CH-7 at 70 eV. Elemental analyses for C, H, and N were performed using a Heraeus CHN-O-Rapid analyzer. All chemicals and solvents were purchased from Merck (Germany) and used without further purification. Two derivatives of [1, 3, 4] thiadiazolo[3,2-*a*]pyrimidin-5-one, and SFIL were prepared with known methods [55, 56].

Synthesis of 1-(4-sulfonic acid) butyl-3-methylimidazolium hydrogen sulfate (SFIL)

A mixture of methylimidazole (10 mmol) and 1,4-butanesultone (10 mmol) was placed on a stirrer at room temperature for 4 days. Then the salt obtained in this step was washed with ether, filtered, and dried under a vacuum. Next, 10 mmol of sulfuric acid 98% was slowly added to the intermediate salt at 0 °C. Then the reaction mixture was stirred for 2 h at 80 °C. Finally, the final product was washed with diethyl ether and dried at 50 °C for 2 h, and the ionic liquid $[MIM(CH_2)_4SO_3H][HSO_4]$ was obtained.

General procedure for the synthesis of 4

A mixture of dimedone or 1,3-cyclohexanedione **3** (1.0 mmol), aldehyde **2** (1.0 mmol), [1, 3, 4] thiadiazolo[3,2-*a*]pyrimidin-5-one **1** (1.0 mmol), and SFIL (10 mol%) and EG (0.5 mL) was stirred at 100 °C for the indicated time (Table 3). The reaction mixture was cooled to room temperature, and a mixture of MeOH: H_2O (2:1), (3 mL) was added to the reaction mixture and the solid residue was collected by filtration, washed with MeOH: H_2O (3*3 mL), and then, dried to give the pure products **3a–3 l.**

2-Benzyl-7,7-dimethyl-10-phenyl-7,8-dihydrochromeno[2,3-*d*][1,3,4] thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4a)

Yellow solid; (0.33 g, 70%) mp: 243–244 °C; IR (KBr) (υ_{max}/cm^{-1}): 3067, 2957, 1696, 1653, 1576, 1534, 1214; ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 0.98 (3H, s, CH_3), 1.08 (3H, s, CH_3), 2.15, 2.33 (2H, AB-quartet system, J_{AB} = 15 Hz, CH_2), 2.65 (2H, s, CH_2), 4.43 (2H, s, CH_2-Ph), 4.85 (1H, s, CH), 7.15–7.40 (10H, m, CH-Ar); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 27.1, 28.98, 32.5, 33.8, 36.6, 50.5, 100.0, 114.0, 127.0, 128.1, 128.5, 128.6, 129.4, 129.7, 135.86, 143.8, 156.4, 158.6, 161.3, 162.8, 164.0, 196.3; MS: (m/z, %): 469 (M^+,87), 390 (95), 349 (85), 333 (82), 168 (26), 91 (68), 28 (100). Anal. Calcd for $C_{27}H_{23}N_3O_3S$ (469.15): C, 69.06; H, 4.94; N, 8.95%. Found: C, 68.82; H, 4.78; N, 8.86%.

2-Benzyl-7,7-dimethyl-10-(*p*-tolyl)-7,8-dihydrochromeno[2,3-*d*][1,3,4] thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4b)

White solid; (0.34 g, 70%) mp: 244–245 °C; IR (KBr) (υ_{max}/cm^{-1}): 3051, 29.55, 1697, 1652, 1573, 1532, 1212; ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm) 0.98 (3H, s, CH_3), 1.07 (3H, s, CH_3), 2.15, 2.32 (2H, AB-quartet system, J_{AB} = 15 Hz, CH_2), 2.21 (3H, s, CH_3), 2.63 (2H, s, CH_2), 4.43 (2H, s, CH_2-benzyl), 4.81 (1H, s, CH), 7.03 (2H, d, $^3J_{HH}$ = 9, CH-Ar), 7.14 (2H, d, $^3J_{HH}$ = 6, CH-Ar), 7.30–7.41 (5H, m, CH-Ar); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 21.0, 27.13, 29.0, 32.5, 33.4, 36.7, 50.5, 100.2, 114.1, 128.1, 128.5, 129.0, 129.4, 129.7, 135.9, 136.1, 140.9, 156.4, 158.5, 161.1, 162.7, 163.8, 196.3; MS: (m/z, %): 484 (M^+,30), 389 (40), 363 (32), 167 (30), 90 (50), 40 (60), 28 (100). Ana. Calcd for $C_{28}H_{25}N_3O_3S$ (483.16): C, 69.54; H, 5.21; N, 8.69%. Found: C, 69.31; H, 4.95; N, 8.50%.

2-Benzyl-10-(4-hydroxyphenyl)-7,7-dimethyl-7,8-dihydrochromeno[2,3-*d*][1,3,4] thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4c)

Yellow solid; (0.345 g, 75%) mp: 247–248 °C; IR (KBr) (υ_{max}/cm^{-1}): 3443 (OH), 3063, 2969, 1696, 1652, 1578, 1536, 1214; ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm): 0.98 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.76 (1H, s, OH), 2.15, 2.31 (2H, AB-quartet system, J_{AB} = 18 Hz, CH_2), 2.62 (2H, s, CH_2), 4.43 (2H, s, CH_2-benzyl), 4.75 (1H, s, CH), 6.62 (2H, d, $^3J_{HH}$ = 9, CH-Ar), 7.03 (2H, d, $^3J_{HH}$ = 9, CH-Ar), 7.32–7.41 (5H, m, CH-Ar); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 27.1, 29.0, 32.4, 32.8, 36.7, 50.6, 100.5, 114.4, 115.2, 128.1, 129.4, 129.5, 129.7, 134.2, 135.9, 156.4, 156.6, 158.5, 160.9, 162.7, 163.6, 196.3; MS: (m/z, %): 486 (M^+,78), 390 (80), 365 (80), 333 (38), 116 (30), 90 (80), 65 (40), 28 (100). Ana. Calcd for $C_{27}H_{23}N_3O_4S$ (485.14): C, 66.79; H, 4.77; N, 8.65%. Found: C, 66.85; H, 4.64; N, 8.91%.

2-Benzyl-10-(4-methoxyphenyl)-7,7-dimethyl-7,8-dihydrochromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4d)

Yellow solid; (0.38 g, 75%) mp: 237–238 °C; IR (KBr) (υ_{max}/cm^{-1}): 3002, 2957, 1697, 1652, 1574, 1531, 1210; ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm): 0.98 (3H, s, CH_3), 1.07 (3H, s, CH_3), 1.72 (3H, s, OMe), 2.15, 2.32 (2H, AB-quartet system, J_{AB} = 15 Hz, CH_2), 2.64 (2H, s, CH_2), 4.43 (2H, s, CH_2-benzyl), 4.79 (1H, s, CH), 6.80 (2H, d, $^3J_{HH}$ = 9, CH-Ar), 7.16 (2H, d, $^3J_{HH}$ = 9, CH-Ar), 7.32–7.40 (5H, m, CH-Ar); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 24.8, 27.14, 29.0, 32. 5, 32.9, 36.6, 50.5, 55.5, 100.3, 113.8, 114.1, 128.1, 129.4, 129.7, 135.9, 136.0, 156.4, 158.3, 158.5, 161.1, 162.8, 163.8, 196.3; MS: (m/z, %): 499 (M$^+$,30), 390 (32), 379 (50), 333 (18), 116 (100), 90 (95), 76 (60), 51 (70), 28 (98). Ana. Calcd for $C_{28}H_{25}N_3O_4S$ (499.16): C, 67.32; H, 5.04; N, 8.41%. Found: C, 67.06; H, 4.81; N, 8.13%.

2-Benzyl-10-(5-bromo-2-hydroxyphenyl)-7,7-dimethyl-7,8-dihydrochromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4e)

Yellow solid; (0.37 g, 65%) mp: 298–300 °C; IR (KBr) (υ_{max}/cm^{-1}): 3417 (OH), 3059, 2955, 1647, 1628, 1571, 1496, 1238; ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm): 1.04 (6H, s, 2CH_3), 1.78 (1H, s, OH), 2.02, 2.20 (2H, AB-quartet system, J_{AB} = 15 Hz, CH_2), 2.40 (2H, dd, $^4J_{HH}$ = 18, CH_2), 4.22 (2H, s, CH_2-benzyl), 5.18 (1H, s, CH), 6.89 (1H, d, $^3J_{HH}$ = 9, CH-Ar), 7.21 (1H, d, $^3J_{HH}$ = 9, CH-Ar), 7.28–7.40 (6H, m, CH-Ar); ^{13}C NMR (75.46 MHz, DMSO-d6): δ (ppm): 27.3, 27.6, 29.6, 32.1, 36.8, 41.1, 51.2, 104.1, 111.4, 115.5, 117.8, 127.8, 129.3, 129.4, 130.8, 131.2, 136.7, 143.1 149.5, 155.2, 158.2, 165.0, 168.8, 176.68, 196.4; MS: (m/z, %): 304 + 258 (M$^+$,15), 287 (88), 208 (20), 180 (20), 148 (45), 116 (18), 91 (38), 43 (70), 28 (100). Ana. Calcd for $C_{27}H_{22}BrN_3O_4S$ (565.05): C, 57.45; H, 3.93; N, 7.44%. Found: C, 57.27; H, 3.75; N, 7.18%.

7,7-Dimethyl-2,10-diphenyl-7,8-dihydrochromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4f)

Yellow solid; (0.32 g, 70%) mp: 276–277 °C;; IR (KBr) (υ_{max}/cm^{-1}): 3064, 2955, 1699, 1655, 1572, 1524, 1214; ^{1}H NMR (300.13 MHz, DMSO-d$_6$): δ (ppm): 1.01 (3H, s, CH_3), 1.10 (3H, s, CH_3), 2.18, 2.35 (2H, AB-quartet system, J_{AB} = 15 Hz, CH_2), 2.70 (2H, s, CH_2), 4.89 (1H, s, CH), 7.16–7.30 (5H, m, CH-Ar), 7.64–7.70 (3H, m, CH-Ar), 7.95–7.99 (2H, m, CH-Ar); ^{13}C NMR (75.46 MHz, DMSO-d$_6$): δ (ppm): 27.2, 29.0, 32.5, 33.9, 50.5, 100.2, 114.0, 127.1, 127.9, 128.48, 128.7, 130.2, 133.5, 143.8, 152.3 156.5, 158.7, 159.1, 160.9, 164.1, 196.3; MS: (m/z, %): 455 (M$^+$,30), 375 (60), 349 (30), 319 (20), 307 (16), 102 (16), 76 (14), 43 (35), 28 (85). Ana. Calcd for $C_{26}H_{21}N_3O_3S$ (455.13): C, 68.55; H, 4.65; N, 9.22%. Found: C, 68.26; H, 4.40; N, 9.20%.

7,7-Dimethyl-2-phenyl-10-(thiophen-2-yl)-7,8-dihydrochromeno[2,3-*d*][1,3,4] thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4 g)

White solid; (0.37 g, 80%) mp: 273–274 °C; IR (KBr) (υ_{max}/cm^{-1}): 3068, 2958, 1699, 1656, 1573, 1525, 1214; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm): 1.09 (6H, d, $J = 3$, $2CH_3$), 2.27 (2H, s, CH_2), 2.52, 2.59 (2H, AB-quartet system, $J_{AB} = 18$ Hz, CH_2), 5.48 (1H, s, CH), 6.78–6.82 (1H, m, CH-thienyl group), 7.00 (1H, d, $^3J_{HH} = 6$, CH-thienyl group), 7.08 (1H, d, $^3J_{HH} = 3$, CH-thienyl group), 7.41–7.54 (3H, m, CH-Ar), 7.83–7.86 (2H, d, CH-Ar); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 27. 7, 28.6, 29.3, 32.3, 40.9, 50.8, 100.7, 114.3, 124.0, 125.8, 127.0, 127.7, 128.1, 129.5, 133.1, 146.7, 156.4, 158.4, 159.0, 159.8, 163.4, 195.9; MS: (m/z, %): 461 (M^+,85), 375 (18), 355 (84), 319 (10), 271 (12), 102 (30), 84 (30), 42 (32), 28 (100). Ana. Calcd for $C_{24}H_{19}N_3O_3S_2$ (461.09): C, 62.45; H, 4.15; N, 9.10%. Found: C, 62.22; H, 3.91; N, 9.06%.

7,7-Dimethyl-10-(naphthalen-2-yl)-2-phenyl-7,8-dihydrochromeno[2,3-*d*][1,3,4] thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4 h)

Yellow solid; (0.39 g, 78%) mp: 287–288 °C; IR (KBr) (υ_{max}/cm^{-1}): 3060, 2959, 1698, 1654, 1574, 1524, 1214; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm): 1.13 (3H, s, CH_3), 1.20 (3H, s, CH_3), 2.26, 2.35 (2H, AB-quartet system, $J_{AB} = 15$ Hz, CH_2), 2.67, 2.74 (2H, AB-quartet system, $J_{AB} = 18$ Hz, CH_2), 5.36 (1H, s, CH), 7.40–7.62 (6H, m, CH-Ar), 7.74–7.91 (6H, m, CH-Ar); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 27.6, 29.2, 32.4, 34.1, 41.0, 50.76, 101.2, 114.6, 125.6, 125.8, 126.8, 127.4, 127.5, 127.6, 127.9, 128.0, 128.1, 129.5, 132.6, 133.1, 133.4, 140.4, 156.5, 158.5, 158.8, 159.7, 163.1, 196.0; MS: (m/z, %): 505 (M^+,70), 399 (50), 375 (60), 318 (18), 270 (8), 126 (8), 102 (10), 28 (100). Ana. Calcd for $C_{30}H_{23}N_3O_3S$ (505.15): C, 71.27; H, 4.59; N, 8.31%. Found: C, 70.99; H, 4.47; N, 8.30%.

7,7-Dimethyl-2-phenyl-10-(m-tolyl)-7,8-dihydrochromeno[2,3-*d*][1,3,4] thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4i)

Yellow solid; (0.33 g, 70%) mp: 239–240 °C; IR (KBr) (υ_{max}/cm^{-1}): 3064, 2962, 1699, 1674, 1655, 1570, 1210; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm): 1.02 (3H, s, CH_3), 1.10 (3H, s, CH_3), 2.18, 2.33 (2H, AB-quartet system, $J_{AB} = 15$ Hz, CH_2), 2.26 (3H, s, CH_3), 2.70 (2H, s, CH_2), 4.85 (1H, s, CH), 6.97 (1H, d, $^3J_{HH} = 9$, CH-Ar), 7.06–7.09 (1H, m, CH-Ar), 7.12–7.18 (2H, m, CH-Ar), 7.61–7.68 (3H, m, CH-Ar), 7.95–7.98 (2H, m, CH-Ar); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 21.5, 27.2, 29.0, 32.5, 33.8, 50.6, 100.3, 114.0, 125.8, 127.7, 127.9, 128.4, 128.5, 129.3, 130.2, 133.5, 137.4, 143.7, 156.8, 158.6, 159.1, 160.8, 164.1, 196.3; MS: (m/z, %): 469 (M^+,88), 374 (95), 362 (80), 347 (45), 319 (75), 270 (25), 120 (22), 103 (74), 77 (52), 44 (40), 28 (100). Ana. Calcd for $C_{27}H_{23}N_3O_3S$ (469.15): C, 69.06; H, 4.94; N, 8.95%. Found: C, 68.78; H, 4.68; N, 8.93%.

2-phenyl-10-(thiophen-2-yl)-7,8-dihydrochromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*] pyrimidine-9,11(6*H*,10*H*)-dione (4j)

Yellow solid; (0.32 g, 75%) mp: 308–310 °C; IR (KBr) (υ_{max}/cm^{-1}): 3092, 2924, 1694, 1659, 1574, 1234; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm): 2.03–2.09 (2H, m, CH_2), 2.36–2.43 (2H, m, CH_2), 2.63–2.74 (2H, m, CH_2), 5.50 (1H, s, CH), 6.78–6.82 (1H, m, CH-thienyl group), 7.01 (1H, d, $^3J_{HH}$ = 6, CH-thienyl group), 7.06 (1H, d, $^3J_{HH}$ = 3, CH-thienyl group), 7.42–7.51 (3H, m, CH-Ar), 7.84–7.86 (2H, d, $^3J_{HH}$ = 6, CH-Ar); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 22.58, 23.75, 24.96, 32.18, 95.98, 110.74, 119.25, 120.89, 122.28, 122.93, 123.35, 124.75, 128.38, 142.04, 151.72, 153.59, 154.22, 155.06, 160.16, 191.20; MS: (m/z, %): 433 (M^+, 65), 347 (20), 327 (60), 102 (22), 71 (20), 42 (40), 28 (100). Ana. Calcd for $C_{22}H_{15}N_3O_3S_2$ (433.06): C, 60.95; H, 3.49; N, 9.69%. Found: C, 61.03; H, 3.55; N, 9.73%.

2-benzyl-10-(p-tolyl)-7,8-dihydrochromeno[2,3-*d*][1,3,4]thiadiazolo[3,2-*a*] pyrimidine-9,11(6*H*,10*H*)-dione (4 k)

White solid; (0.36 g, 80%) mp: 224–226 °C; IR (KBr) (υ_{max}/cm^{-1}): 3063, 3039, 1708, 1650, 1574, 1525, 1206; ^{1}H NMR (300.13 MHz, DMSO-d_6): δ (ppm) 2.05–2.09 (2H, m, CH_2), 2.29 (3H, s, CH_3), 2.39, 2.45 (2H, m, CH_2), 2.71–2.78 (2H, m, CH_2), 4.26, 4.33 (2H, AB-quartet system, J_{AB} = 15 Hz, CH_2-benzyl), 5.16 (1H, s, CH), 7.07 (2H, d, $^3J_{HH}$ = 6, CH-Ar), 7.28–7.42 (8H, m, CH-Ar); ^{13}C NMR (75.46 MHz, DMSO-d_6): δ (ppm): 20.36, 21.12, 27.24, 33.22, 36.94, 37.72, 101.24, 115.89, 128.28, 128.43, 129.01, 129.47, 134.30, 136.53, 140.11, 156.50, 158.37, 160.05, 162.26, 164.60, 196.15; MS: (m/z, %): 455 (M^+,). 455 (30), 375 (60), 319 (20), 76 (20), 43 (40), 28 (80). Ana. Calcd for $C_{26}H_{21}N_3O_3S$ (455.13): C, 68.55; H, 4.65; N, 9.22%. Found: C, 68.33; H, 4.45; N, 9.13%.

10-(naphthalen-2-yl)-2-phenyl-7,8-dihydrochromeno[2,3-*d*][1,3,4] thiadiazolo[3,2-*a*]pyrimidine-9,11(6*H*,10*H*)-dione (4 l)

Yellow solid; (0.31 g, 65%) mp: 330–332 °C; IR (KBr) (υ_{max}/cm^{-1}): 3035, 2921, 1699, 1677, 1575, 1529, 1185; ^{1}H NMR (300.13 MHz, $CDCl_3$): δ (ppm): 2.00–2.07 (2H, m, CH_2), 2.33–2.37 (2H, m, CH_2), 2.68–2.80 (2H, m, CH_2), 5.28 (1H, s, CH), 7.31–7.53 (6H, m, CH-Ar), 7.65–7.82 (6H, m, CH-Ar); ^{13}C NMR (75.46 MHz, $CDCl_3$): δ (ppm): 20.39, 27.34, 34.00, 36.94, 101.21, 115.87, 125.60, 125.81, 126.84, 127.31, 127.52, 127.62, 127.95, 128.01, 128.10, 129.47, 132.63, 133.07, 133.34, 140.49, 156.51, 158.45, 158.80, 159.73, 164.67, 196.16; MS: (m/z, %): 477 (M^+,62), 420 (10), 370 (60), 347 (62), 313 (30), 126 (28), 102 (55), 28 (100). Ana. Calcd for $C_{28}H_{19}N_3O_3S$ (477.11): C, 70.42; H, 4.01; N, 8.80%. Found: C, 70.14; H,3.89; N, 8.92%.

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Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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