Design, Synthesis and Antibacterial Activity of Novel Pyrimidine-Containing 4H-Chromen-4-one Derivatives

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Abstract

A series of pyrimidine-containing 4*H*-chromen-4-one derivatives were designed and synthesized by combining bioactive substructures. All compounds were characterized using ^1H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. Preliminary biological activity results showed that most of title compounds displayed significant inhibitory activity against *Xanthomonas axonopodis* pv. *Citri* (*Xac*), *Xanthomonas oryzae* pv. *oryzae* (*Xoo*) and *Ralstonia solanacearum* (*Rs*). In particular, compound **4c** demonstrated a good inhibitory effect against *Xac* and *Xoo*, with half-maximal effective concentration (EC_{50}) values of 15.5 and 14.9 $\mu\text{g/mL}$ respectively, and that of compound **4h** showed the best antibacterial activity against *Rs* with an EC_{50} value of 14.7 $\mu\text{g/mL}$. These results were better than both bismethiazol (BT, 51.7, 70.1 and 52.7 $\mu\text{g/mL}$, respectively) and thiodiazole copper (TC, 77.9, 95.8 and 72.1 $\mu\text{g/mL}$ respectively). *In vivo* antibacterial activity results indicated that compound **4c** displayed better curative (42.4%) and protective (49.2%) activities for reducing rice bacterial leaf blight than both BT (35.2, 39.1%) and TC (30.8, 27.3%). The mechanism of compound **4c** against *Xoo* was analysed through scanning electron microscopy (SEM). Results showed that the compound destroyed the bacterial cell membrane structure. These results indicated that pyrimidine-containing 4*H*-chromen-4-one derivatives are valuable in the research of new agrochemicals.

Background

One of the main causes of plant diseases is bacterial infection, which causes a large amount of losses to the yield of economic crops every year. Such as, the citrus canker, tobacco bacterial wilt and rice bacterial leaf blight were caused by *Xanthomonas axonopodis* pv. *citri* (*Xac*), *Ralstonia solanacearum* (*Rs*) and *Xanthomonas oryzae* pv. *oryzae* (*Xoo*), respectively [1–3]. It was very serious and hard to manage effectively in agricultural production. Therefore, to protect crops from bacterial infection, the agrochemical (bismethiazol, thiodiazole-copper and azoxy strobil) were used to prevent bacterial infection [4, 5], but prolonged and abuse of traditional chemical pesticides not only enhances the resistance of the bacterial but also harmful to the environment and human health [6–8]. So, exploring novel highly-efficient, broad-spectrum and environmentally benign antibacterial agents is still an arduous task in pesticide science.

3,5,7-Trihydroxy-2-(3,4,5-trihydroxyphen-yl)-4*H*-chromen-4-one (called "myricetin") (Fig. 1A) belongs to a class of natural product that widely found in fruits, vegetables, and herbs, which has attracted more and more researchers due to the unique chemical structure and diverse biological activities [9]. Pharmacological research shows that myricetin and its derivatives present antiviral [10, 11], antibacterial [12–14], antioxidation [15, 16], anticancer [17–19], anti-inflammatory [20] and other biological properties, but most of them are limited to the field of medicine and have few applications in agriculture. In previous work, myricetin was took as the lead compound and active fragments were introduced, a mass of myricetin derivatives with significant biological activity have been discovered. In 2017, Zhong described myricetin derivatives containing 1,3,4 thiadiazole structure, which displayed good inhibitory effect on phytopathogenic bacteria [21]. Recently, Jiang reported a series of dithiocarbamate-containing 4*H*-chromen-4-one derivatives with good *in vitro* antibacterial activity against *Xac* and *Xoo*, with an EC_{50} values are 0.11 $\mu\text{g/mL}$ and 1.58 $\mu\text{g/mL}$, respectively, which were far better than commercial agents bismethiazol and thiodiazole copper [22].

Pyrimidine is an important class of heterocyclic compounds with wide applications in medicine and pesticides research due to their remarkable biological and pharmacological properties, such as antibacterial [23–25],

antiviral [26, 27], insecticide [28, 29], anticancer [30, 31], antimalaria[32], herbicida [33] and other biological activities[34]. In 2019, Zhang reported a series of derivatives containing pyrimidine ethers were synthesized, which have a good control effect on cucumber downy mildew [35]. Recently, Bai described some pyrimidine derivatives with significantly inhibitory efficiencies against Gram-positive bacteria, Gram-negative bacteria and the fungus *Candida albicans* [36].

To develop novel, highly efficient and environment friendly bactericides, we introduced the pyrimidine moiety into 4*H*-chromen-4-one, and a variety of pyrimidine-containing 4*H*-chromen-4-

one derivatives were synthesized and their antibacterial activity were evaluated.

Results And Discussion

Chemistry

The structure of title compounds **4a-4x** were characterized by ^1H NMR, ^{13}C NMR, ^{19}F NMR and HRMS. In ^1H NMR spectra, multiplet signals at δ 8.00–6.50 ppm show the presence of protons in aromatic nucleuses, and a singlet at δ 4.00–3.70 ppm reveals the presence of $-\text{OCH}_3$ group, the $-\text{O}-\text{CH}_2-$ and $-\text{S}-\text{CH}_2-$ characteristic groups between the 4*H*-chromen-4-one skeleton and the substituted pyrimidine were observed at 4.10–3.37 ppm. The chemical shifts at 172.57–160.77 ppm 109.12–106.14 ppm, 27.80–32.12 ppm in the ^{13}C NMR spectra confirmed the existence of $\text{C}=\text{O}$, $-\text{CN}$ and $-\text{CH}_2-$ groups, respectively. The HRMS spectra of title compounds show absorption signals of $[\text{M} + \text{H}]^+$ ions that is consistent with their molecular weight.

X-ray crystal structure of title compounds **4 g**

To further confirm the structures of title compounds, compound **4 g** was successfully cultured a single crystal and studied by single-crystal X-ray analysis as a representative example. The tested single crystal was crystallized from DMSO and acetone mixture solution containing compound **4 g**. As shown in Fig. 3B, C00T-H...O007 and O00R...H-C00R are two important intramolecular hydrogen bonds that combine with 4*H*-chromen-4-one and pyrimidine heterocycle fragments to construct the main molecular scaffold of target compound **4 g**. Besides, as presented in Fig. 3C, four intermolecular hydrogen bonds (O008...H-C011, C00J...H-C00L, C00J...C00L-H, C011-H...O008) between neighboring molecules are primary forces for establishing the three-dimensional structure of target compound **4 g**. crystallographic data listed in Table 1. The deposition number is CCDC 2022970.

Table 1
Crystal data of title compound 4 g.

Crystal Data	
$C_{34}H_{30}BrN_3O_9S$	Colourless/ block
Mr = 736.57	$\rho = 1.430$
triclinic / P-1	Z = 2
a = 12.025(3) [Å]	$\alpha = 103.276(15) [^\circ]$
b = 12.509(4) [Å]	$\beta = 112.727(15) [^\circ]$
c = 14.791(4) [Å]	$\gamma = 102.837(17) [^\circ]$
F(000) = 832	V = 1873.79(9) [Å ³]
Data Collection	
T _{min} =0.310 T _{max} =0.752	Absorption coefficient: 2.537 [mm ⁻¹]
3580 Independent reflections	$\theta_{min} = 3.870^\circ$, $\theta_{max} = 64.332^\circ$
18889 Reflections collected	-13 < = h <= 13, -14 < = k <= 14, -17 < = l <= 16
Refinement	
438 parameters	R indices (all data) R1 = 0.1186, wR2 = 2964
Goodness-of-fit: 1.090	R indices [I > 2 σ (I)] R1 = 0.0835, wR2 = 2591
$\Delta\rho_{max} = 0.426 \text{ eÅ}^{-3}$, $\Delta\rho_{min} = -0.750 \text{ eÅ}^{-3}$	

Antibacterial activity of the title compounds against *Xac*, *Xoo* and *Rs* in vitro

The *in vitro* antibacterial activities of title compounds **4a-4x** against *Xac*, *Xoo* and *Rs* were determined using turbidimeter tests [37, 38]. and the bismethiazol, thiadiazole copper, and myricetin were tested as the control. Preliminary bioassays results in Table 2 indicated that Some compounds with good antibacterial activity against *Xac*, *Xoo* and *Rs*, Among them, compounds **4b**, **4c**, **4 h** and **4o** against *Xac* at 100 and 50 µg/mL with the inhibition rates of 80.4 and 51.4%, 91.3 and 69.0%, 85.3 and 51.4%, 83.2 and 50.5%, respectively, which were better than that of BT (64.6 and 43.4%), TC(55.0 and 34.6%) and myricetin(44.9 and 27.5%). The inhibitory rates of compounds **4c**, **4 h**, **4n** and **4p** indicated against *Xoo* at 100 µg/mL were 89.7, 81.2, 78.3 and 80.7%, respectively, which were superior to that of BT (63.9%), TC (49.5%) and myricetin (44.0%). Note that the inhibition rates of **4c**, **4d**, **4 h**, **4n**, **4o**, **4p** and **4x** against *Xoo* at 50 µg/mL were 72.1, 41.7, 56.0, 54.7, 49.5, 56.0 and 45.6%, respectively, which were superior to those of bismethiazol (44.5%), thiadiazole copper (36.5%) and myricetin (33.3%). Furthermore, **4c**, **4d**, **4 h**, **4 k** **4 l**, **4o** and **4w** have fine antibacterial activity against *Rs* at 100 µg/mL with the inhibition rates of 90.9, 83.9, 92.7, 88.7, 83.2, 90.4 and 80.6%, which were better than those of BT (71.7%), TC (60.1%) and myricetin (50.7%). Similarly, the percentage inhibition of **4c**, **4 h**, **4 k**, **4o** and **4w** against *Rs* at 50 µg/mL were 72.5, 76.2, 66.3, 71.9 and 59.0%, which exceeded BT (52.4%), TC (41.3%) and myricetin (29.6%).

Table 2
Antibacterial activities of title compounds (4a-4x) against Xac, Xoo and Rs in vitro

Compd.	R	n	<i>Xac</i> (%)		<i>Xoo</i> (%)		<i>Rs</i> (%)	
			100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL
4a	Ph	3	37.9 ± 2.8	25.6 ± 1.8	26.3 ± 1.6	13.6 ± 2.0	50.5 ± 0.6	39.2 ± 2.2
4b	3-CH ₃ -Ph	3	80.4 ± 0.3	51.4 ± 0.9	20.7 ± 2.4	13.1 ± 4.2	46.9 ± 1.6	32.1 ± 2.1
4c	4-CH ₃ -Ph	3	91.3 ± 0.6	69.0 ± 1.4	89.7 ± 0.9	72.1 ± 1.8	90.9 ± 1.7	72.6 ± 2.2
4d	4-OCH ₃ -Ph	3	76.7 ± 3.5	40.9 ± 1.6	75.1 ± 0.8	41.70 ± 2.4	83.9 ± 1.4	51.2 ± 0.3
4e	3-Cl-Ph	3	28.7 ± 4.2	20.4 ± 2.6	50.3 ± 3.7	24.7 ± 3.0	34.3 ± 4.2	24.5 ± 1.6
4f	4-Cl-Ph	3	39.6 ± 2.9	28.9 ± 2.0	29.8 ± 1.8	18.1 ± 3.7	35.2 ± 3.6	27.9 ± 1.2
4 g	4-Br-Ph	3	25.3 ± 3.3	16.7 ± 3.1	31.2 ± 3.9	22.1 ± 5.4	67.0 ± 0.9	40.8 ± 1.2
4 h	3-F-Ph	3	85.3 ± 0.7	51.4 ± 2.0	81.3 ± 0.6	56.0 ± 2.2	92.8 ± 0.6	76.3 ± 1.2
4i	4-F-Ph	3	26.4 ± 2.0	25.6 ± 1.0	26.6 ± 2.1	12.5 ± 0.7	37.4 ± 5.6	19.7 ± 4.0
4j	thiophen-2-yl	3	73.5 ± 0.8	41.9 ± 1.6	45.2 ± 2.1	21.8 ± 5.6	51.2 ± 1.1	30.2 ± 1.3
4 k	furan-2-yl	3	31.5 ± 2.7	24.2 ± 1.7	32.8 ± 1.9	21.5 ± 1.6	88.7 ± 1.4	66.4 ± 0.31
4 l	pyridin-4-yl	3	32.2 ± 1.7	21.96 ± 5.1	58.9 ± 1.7	32.5 ± 3.1	83.2 ± 1.6	50.9 ± 2.3
4 m	Ph	4	47.1 ± 3.2	26.4 ± 2.2	47.7 ± 1.1	28.7 ± 1.9	51.8 ± 2.7	25.1 ± 1.3
4n	3-CH ₃ -Ph	4	77.4 ± 1.5	42.9 ± 3.2	78.4 ± 0.6	54.7 ± 2.1	28.5 ± 3.4	17.7 ± 1.6
4o	4-CH ₃ -Ph	4	83.3 ± 0.8	50.5 ± 2.3	74.9 ± 0.3	49.6 ± 2.1	90.4 ± 0.4	72.0 ± 0.9
4p	4-OCH ₃ -Ph	4	27.1 ± 1.9	20.3 ± 1.4	80.8 ± 1.7	56.1 ± 2.2	25.9 ± 3.5	14.±5.8
4q	3-Cl-Ph	4	23.7 ± 2.8	19.9 ± 2.8	47.7 ± 1.3	34.4 ± 1.5	48.4 ± 1.2	35.4 ± 1.5
4r	4-Cl-Ph	4	24.5 ± 1.3	16.8 ± 1.5	26.7 ± 2.4	12.8 ± 1.9	62.6 ± 0.7	39.2 ± 2.9
4 s	3-Br-Ph	4	21.9 ± 1.5	14.7 ± 1.4	45.2 ± 1.5	21.1 ± 3.9	22.2 ± 2.5	12.5 ± 3.4
4t	4-Br-Ph	4	20.2 ± 2.5	17.7 ± 1.2	26.3 ± 4.5	21.6 ± 2.4	44.5 ± 3.8	33.0 ± 1.9
4u	3-F-Ph	4	45.5 ± 3.4	29.2 ± 6.3	23.8 ± 5.4	18.5 ± 1.0	53.4 ± 1.7	39.4 ± 2.2
4v	4-F-Ph	4	27.8 ± 1.5	19.7 ± 4.8	32.6 ± 1.9	27.9 ± 3.6	57.5 ± 1.3	37.5 ± 2.7
4w	furan-2-yl	4	29.1 ± 0.8	20.7 ± 1.3	44.4 ± 0.7	28.8 ± 3.0	80.7 ± 1.8	59.1 ± 1.5

Compd.	R	n	<i>Xac</i> (%)		<i>Xoo</i> (%)		<i>Rs</i> (%)	
			100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL	100 µg/mL	50 µg/mL
4x	pyridin-4-yl	4	41.8 ± 3.7	26.2 ± 2.6	68.6 ± 3.5	45.6 ± 2.5	61.9 ± 1.2	33.2 ± 4.4
My ^b			44.9 ± 1.4	27.5 ± 3.01	44.0 ± 1.2	33.3 ± 0.9	50.7 ± 2.3	29.6 ± 1.1
TC ^c			55.0 ± 0.7	34.6 ± 0.9	49.5 ± 0.3	36.5 ± 1.0	60.1 ± 2.1	41.3 ± 2.5
BT ^c			64.6 ± 1.0	43.4 ± 1.4	63.9 ± 1.0	44.5 ± 0.7	71.7 ± 2.0	52.4 ± 1.8
a Average of three replicates.								
b The lead compound of myricetin.								
c The commercial bactericides bismethiazol (BT) and thiodiazole copper (TC).								

Based on the preliminary bioassays results in Table 2, the EC₅₀ values of some target compounds against *Xac*, *Xoo* and *Rs*, were indicated in Table 3, that compounds **4b**, **4c**, **4h** and **4o** exhibited fine antibacterial activities against *Xac*, with EC₅₀ values of 30.8, 15.5, 28.2, and 29.2 µg/mL, respectively, which exceeded BT (51.7 µg/mL), and TC (77.9 µg/mL). **4c**, **4d**, **4h**, **4n** and **4p** demonstrated good inhibitory effects against *Xoo* with an EC₅₀ value of 14.9, 30.6, 23.7, 28.6 and 24.8 µg/mL, which were better than that of BT (70.1 µg/mL) and TC (95.8 µg/mL). Compounds **4c**, **4d**, **4h**, **4k**, **4l** and **4o** have better antibacterial activity against *Rs* with the EC₅₀ values of 16.0, 23.1, 14.7, 17.5, 24.4, 16.0, and 29.4 µg/mL, respectively, which were superior to that of BT (52.8 µg/mL) and TC (72.1 µg/mL).

Table 3
EC50 values of the title compounds against Xac, Xoo and Rs in vitro^a

Tested bacterial	Compds.	Toxic regression equation	r ²	EC ₅₀ /(µg/mL)
Xac	4b	$y = 1.5705 x + 2.6602$	0.9826	30.9 ± 2.0
	4c	$y = 1.9107 x + 2.7256$	0.9912	15.5 ± 1.7
	4d	$y = 1.5736 x + 2.5280$	0.9825	37.2 ± 2.1
	4 h	$y = 1.7100 x + 2.5176$	0.9809	28.3 ± 1.1
	4j	$y = 1.4978 x + 2.6114$	0.9873	39.3 ± 0.9
	4n	$y = 1.6002 x + 2.5541$	0.9947	33.7 ± 2.2
	4o	$y = 1.7781 x + 2.3894$	0.9811	29.4 ± 2.4
	BT ^c	$y = 1.3743 x + 2.6450$	0.9854	51.7 ± 2.0
	TC ^c	$y = 1.3153 x + 2.5117$	0.9822	77.9 ± 1.7
Xoo	4c	$y = 1.4639 x + 3.2826$	0.9906	14.9 ± 0.9
	4d	$y = 1.2237 x + 3.1804$	0.9693	30.7 ± 1.6
	4 h	$y = 1.4072 x + 3.0639$	0.9961	23.8 ± 1.8
	4 m	$y = 1.2358 x + 3.1996$	0.9773	28.6 ± 2.6
	4o	$y = 1.2425 x + 3.1428$	0.9892	31.2 ± 0.9
	4p	$y = 1.3657 x + 3.0943$	0.9978	24.8 ± 1.1
	BT ^c	$y = 1.3199 x + 2.5633$	0.9848	70.1 ± 1.9
	TC ^c	$y = 1.0632 x + 2.8928$	0.9796	95.8 ± 2.7
RS	4c	$y = 1.6321 x + 3.0312$	0.9929	16.1 ± 2.3
	4d	$y = 1.4199 x + 3.0625$	0.9780	23.1 ± 1.3
	4 h	$y = 1.6908 x + 3.0236$	0.9969	14.7 ± 1.2
	4 k	$y = 1.4931 x + 3.1422$	0.9857	17.5 ± 2.0
	4 l	$y = 1.4276 x + 3.0175$	0.9801	24.8 ± 1.0
	4o	$y = 1.5422 x + 3.1423$	0.9926	16.0 ± 1.3
	4w	$y = 1.4597 x + 2.8546$	0.9833	29.5 ± 2.5
	BT ^c	$y = 1.4267 x + 2.5425$	0.9543	52.8 ± 3.3
	TC ^c	$y = 1.2906 x + 2.5962$	0.9821	72.1 ± 2.1
^a Average of three replicates. ^c The commercial agricultural antibacterial agents bismethiazol (BT) and thiodiazole-copper (TC) were used as control agents.				

Structure–activity relationship analysis of the antibacterial activities.

As indicated in Tables 2, Table 3, most of target compounds showed significant antibacterial activities against *Xac*, *Xoo* and *Rs*, the R groups had significant impact on the antibacterial activity, for example, **4c** (n = 3, R = 4-CH₃-Ph), **4h** (n = 3, R = 3-F-Ph), **4o** (n = 4, R = 4-CH₃-Ph) demonstrated a fine inhibitory effect against *Xac* with the EC₅₀ values of 15.5, 28.2 and 29.3 µg/mL, which were better than those of BT (51.7 µg/mL), and TC (77.9 µg/mL) and other substituents. Compounds **4c** (n = 3, R = 4-CH₃-Ph), **4d** (n = 3, R = 4-OCH₃-Ph) and **4p** (n = 4, R = 4-OCH₃-Ph) demonstrated good inhibitory effects against *Xoo* with an EC₅₀ value of 14.9, 23.7 and 24.8 µg/mL, which were better than that of BT (70.1 µg/mL) and TC (95.8 µg/mL). The presence of donor electron groups and heterocycles may effectively enhance the antibacterial activity against *Rs*, such as compounds **4c** (n = 3, R = 4-CH₃-Ph), **4d** (n = 3, R = 4-OCH₃-Ph), **4k** (n = 3, R = furan), **4l** (n = 3, R = pyridyl) and **4o** (n = 4, R = 4-CH₃-Ph) have better antibacterial activity against *Rs* with the EC₅₀ values of 16.0, 23.1, 17.5, 24.4 and 16.0 µg/mL, respectively, which were superior to that of BT (52.8 µg/mL) and TC (72.1 µg/mL). From this analysis, when n = 3, R is 4-CH₃-Ph, 4-CH₃O-Ph, 3-F-Ph, the bioactivity of compounds are higher than that of n = 4, R is 4-CH₃-Ph, 4-CH₃O-Ph, 3-F-Ph, the activity of the para-substituted by -CH₃, -OCH₃ and other group on the benzene is greater than the meta-substituted. Meanwhile, R was substituted with 3-F-Ph groups, the corresponding compound exhibit remarkable antibacterial activities against *Xac*, *Xoo* and *Rs*.

In vivo bioactivity of **4c** against rice bacterial leaf blight

The experiments of **4c** against rice bacterial leaf blight was determined using a leaf-cutting method. Shown in Table 4 and Fig. 4, when the concentration of compound **4c** was 200 µg.mL⁻¹, the curative activity against bacterial blight of rice was 42.4%. This result was better than that of BT (35.2%) and TC (30.8%). Furthermore, compound **4c** demonstrated excellent protection activity against bacterial blight of rice with the percentage inhibition of 49.2%, which was superior to BT (39.1%) and TC (27.3%). These results suggests that compound **4c** effectively prevents the infection of *Xanthomonas oryzae* of rice.

Scanning electron microscopy (SEM) studies

The mechanism of compound against RS and Xoo were analyzed by SEM [39, 40]. As shown in Fig. 5, the surface morphology of *Xoo* were smooth and remains intact without compound to treatment, (Fig. 5A). When the bacteria was treated with compound **4c** at concentration of 50 ppm, bacteria cell membrane began to appear different degrees wrinkled (Fig. 5B). as the concentration of compound increased to 100 ppm, the bacterial cell membrane showed invagination and rupture (Fig. 5C). Therefore, that compound **4c** destroyed the cell membrane structure, to achieve the purpose of antibacterial.

Methods And Materials

Chemistry

All solvents and reagents were purchased from Shanghai Titan Scientific Co., Ltd, and were analytical grade or chemically pure. The melting point of all compounds (**4a-4x**) was determined by the X-4B melting point apparatus ((Beijing Tech Instrument Co, Beijing. China). ¹H NMR, ¹³C NMR and ¹⁹F NMR were obtained on Bruker Ascend-400 spectrometer (Bruker Optics, Germany) Tetramethylsilane (TMS) as internal standard and DMSO was used as solvent; Mass spectral studies were performed on a quadrupole electrostatic field orbitrap mass

spectrograph (Thermo Scientific, USA). The synthetic route of pyrimidine-containing 4*H*-Chromen-4-one derivatives was shown in Scheme 1. Intermediates **1** were prepared according to the reported methods. [26, 41, 42]

General synthesis procedure for intermediate 1.

Based on the previous reported method [41, 42], the ethyl cyanoacetate (5 mmol), substituted aromatic aldehyde (5 mmol), thiourea (5 mmol) and anhydrous K₂CO₃ (7.5 mmol) were added in ethanol (50 mL) then refluxed for about 4–6 h, after the reaction was completed (monitoring the reaction by TLC), mixture was cooled to room temperature and diluted with ice water, a large amount of solids precipitated as the pH was adjusted with glacial acetic acid to weak acidity, solids were filtered and dried with suction, recrystallized with absolute ethanol to obtain Intermediate **1**

General synthesis procedures for intermediate 2

Myricetin as raw material, iodomethane as the methylation reagent and anhydrous K₂CO₃, heated to reflux in DMF and then extracted with methylene chloride, deglycosylation with concentrated hydrochloric acid under reflux in ethanol to prepare 3-hydroxy-3',4',5',5',7- pentamethoxymyricetin (Intermediate **2**).

General synthesis procedures for intermediate 3

Intermediate **2** (2 mmol) and K₂CO₃ (3 mmol) are dissolved in certain amount of *N,N*-dimethylformamide (DMF). After the solution had been stirred at room temperature for 0.5–1 h, the different dibromoalkane (2 mmol) was added and reaction system continued at room temperature for 10 h. Mixture was dispersed in 50 mL ice water when reaction was completed (reaction was monitored by TLC) so a white solid was precipitated, sample was passed through a suction filter to remove the liquid, solid was continuously stirred in a mixed solution of 30 mL petroleum ether and ethyl acetate for 3–4 hours, then filtered and dried under reduced pressure to obtain Intermediate **3**.

General synthesis procedures for title compounds 4

A solution of intermediates **1** (3 mmol), intermediates **3** (3 mmol) and K₂CO₃ (4.5 mmol) in DMF (40 mL) was stirred under reflux for 4–5 h, after reaction was completed (reaction was monitored by TLC), the mixture was cooled to room temperature then poured into 80 mL ice water and extracted with ethyl acetate (3 × 30 mL), organic layer was washed with 5% hydrochloric acid solution, saturated NaHCO₃ aqueous solution, saturated NaCl solution successively and dried with anhydrous Na₂SO₄, solvent was removed under vacuum and crude product was separated by column chromatography with petroleum ether/ethyl acetate (V:V= 1:1) to obtain the title compound **4a**. Based on the similar method, the title compounds **4b–4x** were prepared.

2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4*H*-chromen-3-yl)oxy)propyl)thio)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (**4a**): white solid, m.p. 144.3–145.8 °C; yield: 41.3%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.94 (d, *J* = 7.3 Hz, 2H, Ph-H), 7.56 (d, *J* = 7.0 Hz, 1H, Ph-H), 7.50 (t, *J* = 7.2 Hz, 2H, Ph-H), 7.34 (s, 2H, Ph-H), 6.84 (s, 1H, Ph-H), 6.50 (s, 1H, Ph-H), 4.03 (s, 2H, -O-CH₂CH₂CH₂-), 3.90 (s, 3H, Ph-OCH₃), 3.85 (s, 3H, Ph-OCH₃), 3.81 (s, 6H, 2 × Ph-OCH₃), 3.72 (s, 3H, Ph-OCH₃), 3.39 (s, 2H, -CH₂CH₂CH₂-S-), 2.12 (d, *J* = 5.7 Hz, 2H, -CH₂CH₂CH₂-); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.57, 164.27, 160.77, 158.65, 153.17, 152.21, 140.16, 139.89, 132.18, 129.08,

128.99, 125.94, 116.45, 108.88, 106.12, 96.41, 93.60, 93.39, 70.50, 60.63, 56.57, 56.49, 30.06, 27.80; HRMS calcd for $C_{34}H_{31}N_3O_9S$ $[M + H]^+$: 658.1854, found 658.1851.

2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-6-oxo-4-(m-tolyl)-1,6-dihydropyrimidine-5-carbonitrile (4b): white solid, m.p. 231.6-232.8 °C; yield: 67.2%; 1H NMR (400 MHz, DMSO- d_6) δ 7.71 (s, 2H, Ph-H), 7.37 (d, J = 6.9 Hz, 2H, Ph-H), 7.34 (s, 2H, Ph-H), 6.85 (d, J = 2.2 Hz, 1H, Ph-H), 6.50 (d, J = 2.2 Hz, 1H, Ph-H), 4.02 (t, J = 5.8 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.85 (s, 3H, Ph-OCH₃), 3.80 (s, 6H, 2 × Ph-OCH₃), 3.72 (s, 3H, Ph-OCH₃), 3.34 (s, 2H, O-CH₂CH₂CH₂-S-), 2.31 (s, 3H, Ph-CH₃), 2.15–2.04 (m, 2H, -CH₂CH₂CH₂-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.56, 167.64, 164.26, 160.75, 158.65, 153.16, 152.18, 140.20, 139.82, 138.29, 132.64, 129.49, 128.85, 126.31, 125.94, 108.85, 106.03, 96.41, 93.57, 70.55, 60.63, 56.53, 56.45, 30.17, 27.74, 21.32; HRMS calcd for $C_{35}H_{33}N_3O_9S$ $[M + H]^+$: 672.2010, found 672.1999.

2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-6-oxo-4-(p-tolyl)-1,6-dihydropyrimidine-5-carbonitrile (4c): White solid, m.p. 201.8-203.6 °C; yield: 30.3%; 1H NMR (400 MHz, DMSO- d_6) δ 7.85 (d, J = 8.1 Hz, 2H, Ph-H), 7.35 (s, 2H, Ph-H), 7.27 (d, J = 8.1 Hz, 2H, Ph-H), 6.85 (d, J = 2.1 Hz, 1H, Ph-H), 6.51 (d, J = 2.1 Hz, 1H, Ph-H), 4.03 (t, J = 5.9 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.91 (s, 3H, Ph-OCH₃), 3.86 (s, 3H, Ph-OCH₃), 3.82 (s, 6H, 2 × Ph-OCH₃), 3.72 (s, 3H, Ph-OCH₃), 3.36 (d, J = 6.5 Hz, 2H, -O-CH₂CH₂CH₂-S-), 2.34 (s, 3H, Ph-CH₃), 2.12 (dd, J = 12.8, 6.3 Hz, 2H, -O-CH₂CH₂CH₂-S-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.57, 166.16, 164.28, 160.78, 158.66, 153.18, 152.18, 142.51, 140.17, 139.90, 132.85, 129.56, 129.18, 125.94, 116.59, 108.90, 106.11, 96.42, 93.61, 92.75, 70.53, 60.61, 56.77, 56.39, 55.39, 30.13, 27.78, 21.51; HRMS calcd for $C_{35}H_{33}N_3O_9S$ $[M + H]^+$: 671.1932, found 671.1905.

2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4d): white solid, m.p. 179.2-181.1 °C; yield: 32.5%; 1H NMR (400 MHz, DMSO- d_6) δ 8.01 (d, J = 8.8 Hz, 2H, Ph-H), 7.35 (s, 2H, Ph-H), 7.02 (d, J = 8.9 Hz, 2H, Ph-H), 6.84 (d, J = 2.2 Hz, 1H, Ph-H), 6.50 (d, J = 2.2 Hz, 1H, Ph-H), 4.04 (t, J = 5.9 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.91 (s, 3H, Ph-OCH₃), 3.86 (s, 3H, Ph-OCH₃), 3.81 (s, 6H, 2 × Ph-OCH₃), 3.80 (s, 3H, Ph-OCH₃), 3.72 (s, 3H, Ph-OCH₃), 3.39 (d, J = 6.9 Hz, 2H, -O-CH₂CH₂CH₂-S-), 2.17–2.07 (m, 2H, -O-CH₂CH₂CH₂-S-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.57, 164.27, 162.66, 160.77, 158.65, 153.17, 152.14, 140.19, 139.90, 131.27, 125.93, 116.88, 114.42, 108.88, 106.09, 96.42, 93.60, 70.51, 60.62, 56.57, 56.52, 56.48, 55.88, 55.39, 30.16, 27.76; HRMS calcd for $C_{35}H_{33}N_3O_{10}S$ $[M + H]^+$: 688.1959, found 688.1952.

4-(3-chlorophenyl)-2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4e): Brown solid, m.p. 119.6-121.9 °C; yield: 23.9%; 1H NMR (400 MHz, DMSO- d_6) δ 7.94–7.84 (m, 2H, Ph-H), 7.62 (d, J = 8.0 Hz, 1H, Ph-H), 7.53 (t, J = 7.9 Hz, 1H, Ph-H), 7.33 (s, 2H, Ph-H), 6.83 (d, J = 1.6 Hz, 1H, Ph-H), 6.50 (s, 1H, Ph-H), 4.02 (t, J = 5.5 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.85 (s, 3H, Ph-OCH₃), 3.81 (s, 6H, 2 × Ph-OCH₃), 3.72 (s, 3H, Ph-OCH₃), 3.35 (d, J = 6.3 Hz, 2H, -O-CH₂CH₂CH₂-S-), 2.13–2.02 (m, 2H, -O-CH₂CH₂CH₂-S-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.58, 165.98, 164.24, 160.75, 158.64, 153.14, 152.19, 140.21, 139.85, 137.87, 133.66, 131.70, 130.91, 128.69, 127.77, 125.96, 108.87, 106.08, 96.39, 93.57, 70.49, 60.63, 56.56, 56.51, 56.47, 30.11, 27.76; HRMS calcd for $C_{34}H_{30}ClN_3O_9S$ $[M + H]^+$: 692.1464, found 692.1455.

4-(4-chlorophenyl)-2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4f**): White solid, m.p. 182.4-183.8 °C; yield: 41.7%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.93 (d, *J* = 8.5 Hz, 2H, Ph-H), 7.55 (d, *J* = 8.5 Hz, 2H, Ph-H), 7.36 (s, 2H, Ph-H), 6.84 (d, *J* = 2.0 Hz, 1H, Ph-H), 6.50 (d, *J* = 2.0 Hz, 1H, Ph-H), 4.03 (t, *J* = 6.0 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.91 (s, 3H, Ph-OCH₃), 3.87 (s, 3H, Ph-OCH₃), 3.83 (s, 6H, 2 × Ph-OCH₃), 3.73 (s, 3H, Ph-OCH₃), 3.28 (d, *J* = 6.9 Hz, 2H, -O-CH₂CH₂CH₂-S-), 2.14–2.06 (m, 2H, -O-CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.59, 166.22, 164.26, 160.76, 158.65, 153.18, 152.15, 140.18, 139.89, 136.55, 135.01, 130.89, 129.03, 125.95, 108.89, 106.09, 96.42, 93.61, 70.60, 60.62, 56.59, 56.50, 30.29, 27.55; HRMS calcd for C₃₄H₃₀ClN₃O₉S [M + H]⁺: 692.1640, found 692.1450.

4-(4-bromophenyl)-2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4g**): White solid, m.p. 183.2-185.1 °C; yield: 25.7%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.88 (d, *J* = 8.5 Hz, 2H, Ph-H), 7.70 (d, *J* = 8.5 Hz, 2H, Ph-H), 7.35 (s, 2H, Ph-H), 6.85 (d, *J* = 1.8 Hz, 1H, Ph-H), 6.51 (d, *J* = 1.7 Hz, 1H, Ph-H), 4.03 (s, 2H, -O-CH₂CH₂CH₂-S-), 3.91 (s, 3H, Ph-OCH₃), 3.87 (s, 3H, Ph-OCH₃), 3.83 (s, 6H, 2 × Ph-OCH₃), 3.73 (s, 3H, Ph-OCH₃), 3.37 (s, 2H, -O-CH₂CH₂CH₂-S-), 2.16–2.06 (m, 2H, -O-CH₂CH₂CH₂-S-). ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.59, 166.41, 164.28, 160.76, 158.65, 153.18, 152.17, 140.14, 139.89, 134.84, 132.08, 131.16, 125.96, 116.36, 108.88, 106.07, 96.43, 93.52, 70.48, 60.63, 56.63, 56.50, 30.16, 27.74; HRMS calcd for C₃₄H₃₀BrN₃O₉S [M + H]⁺: 736.0959, found 736.0927.

2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-4-(3-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4h**): Brown solid, m.p. 204.6-206.4 °C; yield: 57.0%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.78 (d, *J* = 7.8 Hz, 1H, Ph-H), 7.70 (d, *J* = 9.8 Hz, 1H, Ph-H), 7.55 (dd, *J* = 14.0, 8.0 Hz, 1H, Ph-H), 7.40 (td, *J* = 8.5, 2.3 Hz, 1H, Ph-H), 7.34 (s, 2H, Ph-H), 6.83 (d, *J* = 2.1 Hz, 1H, Ph-H), 6.49 (d, *J* = 2.1 Hz, 1H, Ph-H), 4.02 (t, *J* = 5.8 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.85 (s, 3H, Ph-OCH₃), 3.81 (s, 6H, 2 × Ph-OCH₃), 3.72 (s, 3H, Ph-OCH₃), 3.34 (d, *J* = 6.8 Hz, 2H, -O-CH₂CH₂CH₂-S-), 2.16–2.03 (m, 2H, -O-CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.59, 166.00, 164.24, 163.41, 160.98, 160.75, 158.64, 153.15, 152.19, 140.18, 139.85, 131.15, 131.07, 125.95, 125.28, 118.86, 118.66, 116.75, 115.94, 115.71, 108.87, 106.07, 96.39, 93.57, 70.52, 60.62, 56.55, 56.51, 56.46, 30.13, 27.72; ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -112.23 (d, *J* = 6.1 Hz); HRMS calcd for C₃₄H₃₀FN₃O₉S [M + H]⁺: 676.1760, found 676.1755.

2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-4-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (**4i**): White solid, m.p. 197.5-199.4 °C; yield: 31.7%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 8.05 (dd, *J* = 8.1, 5.6 Hz, 2H, Ph-H), 7.39–7.30 (m, 4H, Ph-H), 6.84 (d, *J* = 1.3 Hz, 1H, Ph-H), 6.50 (s, 1H, Ph-H), 4.02 (t, *J* = 5.9 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.91 (s, 3H, Ph-OCH₃), 3.86 (s, 3H, Ph-OCH₃), 3.82 (s, 6H, 2 × Ph-OCH₃), 3.73 (s, 3H, Ph-OCH₃), 3.37 (d, *J* = 6.5 Hz, 2H, -O-CH₂CH₂CH₂-S-), 2.18–2.06 (m, 2H, -O-CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.57, 166.40, 165.71, 164.25, 163.22, 160.72, 158.64, 153.16, 152.16, 140.13, 139.83, 131.99, 131.89, 125.92, 116.46, 116.25, 116.03, 108.85, 106.01, 96.40, 93.58, 93.21, 70.42, 60.61, 56.51, 56.46, 30.10, 27.72; ¹⁹F NMR (376 MHz, DMSO-*d*₆) δ -107.84; HRMS calcd for C₃₄H₃₀FN₃O₉S [M + H]⁺: 676.1760, found 676.1755.

2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-6-oxo-4-(thiophen-2-yl)-1,6-dihydropyrimidine-5-carbonitrile (**4j**): Gray solid, m.p. 145.4-147.8 °C; yield: 50.6%; ¹H NMR (400 MHz,

DMSO- d_6) δ 8.22 (d, J = 3.8 Hz, 1H, thienyl-H), 7.94 (d, J = 5.0 Hz, 1H, thienyl-H), 7.36 (s, 2H, Ph-H), 7.31–7.27 (m, 1H, thienyl -H), 6.82 (d, J = 2.1 Hz, 1H, Ph-H), 6.49 (d, J = 2.1 Hz, 1H, Ph-H), 4.07 (t, J = 6.0 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.85 (s, 3H, Ph-OCH₃), 3.84 (s, 6H, 2 $\times$ Ph-OCH₃), 3.73 (s, 3H, Ph-OCH₃), 3.30 (d, J = 7.0 Hz, 2H -O-CH₂CH₂CH₂-S-), 2.17–2.09 (m, 2H -O-CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO- d_6) δ 172.60, 164.24, 160.75, 158.95, 158.64, 153.16, 152.23, 140.33, 140.17, 139.87, 134.86, 131.58, 129.84, 125.97, 117.16, 108.88, 106.16, 96.40, 93.57, 88.04, 70.60, 60.64, 56.57, 56.51, 30.09, 27.86; HRMS calcd for C₃₃H₂₈N₄O₃[M + H]⁺: 664.1418, found 664.1411.

2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-4-(furan-2-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4 k): Gray solid, m.p. 229.4–231.3 °C; yield: 60.3%; ¹H NMR (400 MHz, DMSO- d_6) δ 8.09 (d, J = 0.8 Hz, 1H, furyl-H), 7.47 (d, J = 3.5 Hz, 1H, furyl-H), 7.36 (s, 2H, Ph-H), 6.83 (d, J = 2.2 Hz, 1H, furyl-H), 6.70 (dd, J = 3.5, 1.7 Hz, 1H, Ph-H), 6.49 (d, J = 2.2 Hz, 1H, Ph-H), 4.06 (t, J = 6.0 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.91 (s, 3H, Ph-OCH₃), 3.86 (s, 3H, Ph-OCH₃), 3.84 (s, 6H, 2 $\times$ Ph-OCH₃), 3.73 (s, 3H, Ph-OCH₃), 3.35 (s, 2H, -O-CH₂CH₂CH₂-S-), 2.15–2.06 (m, 2H, -O-CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO- d_6) δ 172.59, 164.25, 160.77, 158.64, 154.94, 153.17, 152.21, 149.92, 148.42, 140.17, 139.91, 125.94, 118.62, 115.85, 113.63, 108.90, 106.14, 96.41, 93.58, 88.01, 70.64, 60.63, 56.57, 56.51, 55.39, 30.06, 27.81; HRMS calcd for C₃₂H₂₉N₃O₁₀S [M + H]⁺: 648.1646, found 648.1638.

2-((3-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)propyl)thio)-6-oxo-4-(pyridin-4-yl)-1,6-dihydropyrimidine-5-carbonitrile (4 l): Brown solid, m.p. 147.8–149.8 °C; yield: 50.2%; ¹H NMR (400 MHz, DMSO- d_6) δ 8.75 (d, J = 5.8 Hz, 2H, Piperidiny-H), 7.85 (dd, J = 4.5, 1.5 Hz, 2H, Piperidiny-H), 7.34 (s, 2H, Ph-H), 6.84 (d, J = 2.1 Hz, 1H, Ph-H), 6.50 (d, J = 2.1 Hz, 1H, Ph-H), 4.03 (t, J = 6.0 Hz, 2H, -O-CH₂CH₂CH₂-S-), 3.91 (s, 3H, Ph-OCH₃), 3.86 (s, 3H, Ph-OCH₃), 3.82 (s, 6H, 2 $\times$ Ph-OCH₃), 3.73 (s, 3H, Ph-OCH₃), 3.36 (t, J = 7.0 Hz, 2H, -O-CH₂CH₂CH₂-S-), 2.15–2.07 (m, 2H, -O-CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO- d_6) δ 172.58, 167.58, 165.46, 164.28, 160.77, 158.65, 153.18, 152.20, 150.65, 142.98, 140.14, 139.92, 125.93, 122.83, 115.85, 108.89, 106.13, 96.42, 94.67, 93.62, 70.46, 60.65, 56.58, 56.52, 30.01, 27.84; HRMS calcd for C₃₃H₃₀N₄O₉S [M + H]⁺: 659.1806, found 659.1811.

2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-6-oxo-4-phenyl-1,6-dihydropyrimidine-5-carbonitrile (4 m): Yellow solid, m.p. 227.0–228.5 °C; yield: 42.9%; ¹H NMR (400 MHz, DMSO- d_6) δ 7.93–7.87 (m, 2H, Ph-H), 7.56–7.46 (m, 3H Ph-H), 7.33 (m, 2H, Ph-H), 6.83 (d, J = 2.1 Hz, 1H, Ph-H), 6.49 (d, J = 2.0 Hz, 1H, Ph-H), 3.95 (t, J = 5.8 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.84 (s, 3H, Ph-OCH₃), 3.83 (d, J = 5.0 Hz, 6H, 2 $\times$ Ph-OCH₃), 3.74 (s, 3H, Ph-OCH₃), 3.27 (t, J = 6.7 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.81 (dd, J = 14.0, 6.5 Hz, 4H, -O-CH₂CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO- d_6) δ 172.63, 166.53, 164.23, 160.74, 158.62, 153.13, 152.05, 140.27, 139.86, 132.10, 129.03, 128.95, 125.99, 116.44, 108.90, 106.13, 96.38, 93.56, 71.38, 60.65, 56.56, 56.51, 30.44, 29.00, 26.05; HRMS calcd for C₃₅H₃₃N₃O₉S [M + H]⁺: 672.2010, found 672.2007.

2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-6-oxo-4-(m-tolyl)-1,6-dihydropyrimidine-5-carbonitrile (4n): Yellow solid, m.p. 207.6–209.5 °C; yield: 45.8%; ¹H NMR (400 MHz, DMSO- d_6) δ 7.69 (d, J = 8.8 Hz, 2H, Ph-H), 7.41–7.35 (m, 2H, Ph-H), 7.34 (s, 2H, Ph-H), 6.82 (d, J = 2.2 Hz, 1H, Ph-H), 6.49

(d, J = 2.3 Hz, 1H, Ph-H), 3.96 (t, J = 5.7 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.84 (s, 3H, Ph-OCH₃), 3.83 (s, 6H, 2 × Ph-OCH₃), 3.26 (t, J = 6.8 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 2.32 (s, 3H, Ph-OCH₃), 1.88–1.72 (m, 4H, -O-CH₂CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.60, 164.22, 160.74, 158.61, 153.12, 152.03, 140.26, 139.87, 138.30, 132.71, 129.47, 128.84, 126.26, 125.98, 116.41, 108.90, 106.14, 96.36, 93.55, 71.36, 60.64, 56.50, 30.42, 29.01, 26.14, 21.33; HRMS calcd for C₃₆H₃₅N₃O₉S [M + H]⁺: 686.2167, found 686.2161.

2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-6-oxo-4-(p-tolyl)-1,6-dihydropyrimidine-5-carbonitrile (4o): White solid, m.p. 229.8-231.2 °C; yield: 59.1%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.82 (d, J = 8.2 Hz, 2H, Ph-H), 7.35 (s, 2H, Ph-H), 7.27 (d, J = 8.1 Hz, 2H, Ph-H), 6.83 (d, J = 2.2 Hz, 1H, Ph-H), 6.49 (d, J = 2.2 Hz, 1H, Ph-H), 3.97 (t, J = 5.8 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.84 (s, 9H, 3 × Ph-OCH₃), 3.27 (t, J = 6.7 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 2.32 (s, 3H, Ph-OCH₃), 1.81 (dd, J = 11.6, 6.6 Hz, 4H, -O-CH₂CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.62, 167.36, 166.21, 164.23, 160.75, 158.6, 153.12, 151.97, 142.47, 140.26, 139.87, 132.85, 129.51, 129.10, 125.98, 116.57, 108.89, 106.11, 96.37, 93.56, 92.76, 71.33, 60.64, 56.54, 56.51, 30.38, 28.96, 26.12, 21.45; HRMS calcd for C₃₆H₃₅N₃O₉S [M + H]⁺: 686.2167, found 686.2191.

2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-4-(4-methoxyphenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4p): Yellow solid, m.p. 236.4-237.8 °C; yield: 51.9%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.97 (d, J = 8.9 Hz, 2H, Ph-H), 7.35 (s, 2H, Ph-H), 7.04 (d, J = 9.0 Hz, 2H, Ph-H), 6.82 (d, J = 2.2 Hz, 1H, Ph-H), 6.48 (d, J = 2.2 Hz, 1H, Ph-H), 3.97 (t, J = 5.6 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.84 (s, 9H, 3 × Ph-OCH₃), 3.80 (s, 3H, Ph-OCH₃), 3.74 (s, 3H, Ph-OCH₃), 3.28 (t, J = 6.6 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.88–1.76 (m, 4H, -O-CH₂CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.64, 164.2, 162.63, 160.74, 158.59, 153.12, 151.95, 140.28, 139.88, 131.16, 125.98, 116.90, 114.39, 108.87, 106.11, 96.36, 93.55, 71.35, 60.64, 56.51, 55.87, 30.38, 28.99, 26.12; HRMS calcd for C₃₆H₃₅N₃O₁₀S [M]⁺: 701.2038, found 701.2026.

4-(3-chlorophenyl)-2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4q): Yellow solid, m.p. 137.2-139.2 °C; yield: 41.8%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.81 (dd, J = 7.2, 1.3 Hz, 2H Ph-H), 7.59–7.48 (m, 2H, Ph-H), 7.35 (s, 2H, Ph-H), 6.82 (d, J = 2.2 Hz, 1H, Ph-H), 6.49 (d, J = 2.2 Hz, 1H, Ph-H), 3.95 (s, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.84 (s, 9H, 3 × Ph-OCH₃), 3.74 (s, 3H, Ph-OCH₃), 3.16 (s, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.79 (s, 4H, -O-CH₂CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.63, 165.88, 164.21, 160.75, 158.61, 153.12, 152.03, 140.30, 139.86, 133.53, 131.09, 130.76, 128.51, 127.53, 126.01, 108.91, 106.14, 96.36, 93.55, 71.47, 60.64, 56.52, 56.50, 30.24, 29.10, 26.25; HRMS calcd for C₃₅H₃₂ClN₃O₉S [M + H]⁺: 706.1621, found 706.1605.

4-(4-chlorophenyl)-2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4r): Yellow solid, m.p. 129.5-131.8 °C; yield: 61.5%; ¹H NMR (400 MHz, DMSO-*d*₆) δ 7.84 (d, J = 8.6 Hz, 2H, Ph-H), 7.70 (d, J = 8.6 Hz, 2H, Ph-H), 7.35 (s, 2H, Ph-H), 6.83 (d, J = 2.2 Hz, 1H, Ph-H), 6.49 (d, J = 2.2 Hz, 1H, Ph-H), 3.96 (t, J = 5.8 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.91 (s, 3H, Ph-OCH₃), 3.85 (s, 3H, Ph-OCH₃), 3.84 (s, 6H, 2 × Ph-OCH₃), 3.74 (s, 3H, Ph-OCH₃), 3.27 (t, J = 6.8 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.81 (dd, J = 14.8, 6.6 Hz, 4H, -O-CH₂CH₂CH₂CH₂-S-); ¹³C NMR (101 MHz, DMSO-*d*₆) δ 172.65, 166.79, 166.44, 164.24, 160.75, 158.60, 153.13, 151.96, 140.28, 139.90, 134.84, 132.05, 131.06, 125.97, 116.27, 108.88, 106.13, 96.41,

93.59, 71.36, 60.65, 56.57, 56.53, 30.42, 28.93, 26.08; HRMS calcd for $C_{35}H_{32}ClN_3O_9S$ $[M + H]^+$: 706.1621, found 706.1592.

4-(3-bromophenyl)-2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4 s): Yellow solid, m.p. 119.5-121.4 °C; yield: 30.5%; 1H NMR (400 MHz, DMSO- d_6) δ 7.99 (d, J = 1.7 Hz, 1H, Ph-H), 7.90 (d, J = 7.8 Hz, 1H, Ph-H), 7.73 (d, J = 7.9 Hz, 1H, Ph-H), 7.46 (t, J = 7.9 Hz, 1H, Ph-H), 7.35 (d, J = 9.9 Hz, 2H, Ph-H), 6.82 (d, J = 2.1 Hz, 1H, Ph-H, Ph-H), 6.49 (d, J = 1.9 Hz, 1H, Ph-H), 3.96 (s, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.84 (d, J = 3.1 Hz, 12H, 4 × Ph-OCH₃), 3.73 (d, J = 1.8 Hz, 3H, Ph-OCH₃), 3.26 (t, J = 6.5 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.80 (s, 4H, -O-CH₂CH₂CH₂CH₂-S-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.62, 165.89, 164.21, 160.73, 158.60, 153.11, 152.03, 140.26, 139.83, 137.89, 134.64, 131.56, 131.12, 128.06, 125.98, 122.05, 116.14, 108.89, 106.11, 96.36, 93.54, 71.37, 60.64, 56.50, 30.44, 28.97, 26.10; HRMS calcd for $C_{35}H_{32}BrN_3O_9S$ $[M + H]^+$: 750.1115, found 750.1126.

4-(4-bromophenyl)-2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4t): White solid, m.p. 153.6-155.4 °C; yield: 46.1%; 1H NMR (400 MHz, DMSO- d_6) δ 7.86–7.81 (m, 2H, Ph-H), 7.73–7.66 (m, 2H, Ph-H), 7.35 (s, 2H, Ph-H), 6.83 (d, J = 2.2 Hz, 1H, Ph-H), 6.49 (d, J = 2.2 Hz, 1H, Ph-H), 3.96 (t, J = 5.8 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.91 (s, 3H, Ph-OCH₃), 3.85 (s, 3H, Ph-OCH₃), 3.84 (s, 6H, 2 × Ph-OCH₃), 3.74 (s, 3H, Ph-OCH₃), 3.27 (t, J = 6.8 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.81 (dd, J = 14.8, 6.6 Hz, 4H, -O-CH₂CH₂CH₂CH₂-S-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.65, 166.79, 166.44, 164.24, 160.75, 158.60, 153.13, 151.96, 140.28, 139.90, 134.84, 132.05, 131.06, 125.97, 116.27, 108.88, 106.13, 96.41, 93.59, 71.36, 60.65, 56.57, 56.53, 30.42, 28.93, 26.08; HRMS calcd for $C_{35}H_{32}BrN_3O_9S$ $[M + H]^+$: 750.1115, found 750.1108.

2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-4-(3-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4u): White solid, m.p. 119.8-121.64 °C; yield: 70.8%; 1H NMR (400 MHz, DMSO- d_6) δ 7.73 (d, J = 7.9 Hz, 1H, Ph-H), 7.65 (dd, J = 9.8, 2.0 Hz, 1H, Ph-H), 7.55 (td, J = 8.0, 6.1 Hz, 1H, Ph-H), 7.41–7.36 (m, 1H, Ph-H), 7.35 (d, J = 3.9 Hz, 2H, Ph-H), 6.83 (d, J = 2.2 Hz, 1H, Ph-H), 6.48 (d, J = 2.2 Hz, 1H, Ph-H), 3.95 (t, J = 5.5 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.84 (s, 9H, 3 × Ph-OCH₃), 3.73 (s, 3H, Ph-OCH₃), 3.24 (t, J = 6.4 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.80 (d, J = 3.2 Hz, 4H, -O-CH₂CH₂CH₂CH₂-S-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.63, 164.21, 160.94, 160.73, 158.60, 153.12, 152.02, 140.27, 139.84, 131.09, 125.99, 125.22, 115.87, 115.64, 108.88, 106.10, 96.35, 93.53, 71.38, 60.64, 56.51, 30.41, 28.98, 26.04; ^{19}F NMR (376 MHz, DMSO- d_6) δ -112.28; HRMS calcd for $C_{35}H_{32}FN_3O_9S$ $[M + H]^+$: 690.1916, found 690.1915.

2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-4-(4-fluorophenyl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4v): White solid, m.p. 223.0-224.8 °C; yield: 25.3%; 1H NMR (400 MHz, DMSO- d_6) δ 7.99 (dd, J = 8.9, 5.5 Hz, 2H, Ph-H), 7.38–7.32 (m, 4H, Ph-H), 6.84 (d, J = 2.2 Hz, 1H, Ph-H), 6.50 (d, J = 2.2 Hz, 1H, Ph-H), 3.96 (t, J = 5.8 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.84 (d, J = 2.0 Hz, 9H, 3 × Ph-OCH₃), 3.74 (s, 3H, Ph-OCH₃), 3.27 (t, J = 6.7 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.81 (dd, J = 9.6, 4.5 Hz, 4H, -O-CH₂CH₂CH₂CH₂-S-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.67, 164.24, 160.72, 158.61, 153.12, 152.00, 140.27, 139.82, 131.81, 125.98, 116.54, 116.21, 115.99, 108.86, 106.07, 96.40, 93.56, 71.39, 60.64, 56.51, 30.39, 28.97,

26.07; ^{19}F NMR (376 MHz, DMSO) δ -105.82; HRMS calcd for $\text{C}_{35}\text{H}_{32}\text{FN}_3\text{O}_9\text{S}$ $[\text{M} + \text{H}]^+$: 690.1916, found 690.1894

2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-4-(furan-2-yl)-6-oxo-1,6-dihydropyrimidine-5-carbonitrile (4w): Black solid, m.p. 236.8-238.7 °C; yield: 73.2%; ^1H NMR (400 MHz, DMSO- d_6) δ 8.10 (s, 1H, Ph-H), 7.45 (d, J = 3.4 Hz, 1H, Ph-H), 7.36 (d, J = 4.2 Hz, 2H, Ph-H), 6.82 (d, J = 2.2 Hz, 1H, Ph-H), 6.71 (dd, J = 3.5, 1.7 Hz, 1H, Ph-H), 6.49 (d, J = 2.1 Hz, 1H, Ph-H), 4.00 (d, J = 5.2 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.85 (s, 6H, 2 $\times$ Ph-OCH₃), 3.84 (s, 3H, Ph-OCH₃), 3.76–3.72 (m, 3H, Ph-OCH₃), 3.29 (s, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.81 (d, J = 2.9 Hz, 4H, -O-CH₂CH₂CH₂CH₂-S-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.67, 164.22, 160.71, 158.59, 154.86, 153.11, 151.97, 149.77, 148.57, 140.29, 139.80, 125.99, 118.73, 115.71, 113.67, 108.85, 106.03, 96.38, 93.53, 71.34, 60.65, 56.50, 30.29, 28.91, 26.04; HRMS calcd for $\text{C}_{33}\text{H}_{31}\text{N}_3\text{O}_{10}\text{S}$ $[\text{M} + \text{H}]^+$: 662.1803, found 662.1790.

2-((4-((5,7-dimethoxy-4-oxo-2-(3,4,5-trimethoxyphenyl)-4H-chromen-3-yl)oxy)butyl)thio)-6-oxo-4-(pyridin-4-yl)-1,6-dihydropyrimidine-5-carbonitrile (4x): Yellow solid, m.p. 213.8-215.8 °C; yield: 56.6%; ^1H NMR (400 MHz, DMSO- d_6) δ 8.75 (d, J = 5.8 Hz, 2H, Ph-H), 7.81 (dd, J = 4.5, 1.6 Hz, 2H, Ph-H), 7.34 (s, 2H, Ph-H), 6.83 (d, J = 2.2 Hz, 1H, Ph-H), 6.49 (d, J = 2.2 Hz, 1H, Ph-H), 3.95 (t, J = 5.8 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 3.90 (s, 3H, Ph-OCH₃), 3.84 (s, 3H, Ph-OCH₃), 3.83 (s, 6H, 2 $\times$ Ph-OCH₃), 3.73 (s, 3H, Ph-OCH₃), 3.28 (t, J = 6.7 Hz, 2H, -O-CH₂CH₂CH₂CH₂-S-), 1.85–1.75 (m, 4H, -O-CH₂CH₂CH₂CH₂-S-); ^{13}C NMR (101 MHz, DMSO- d_6) δ 172.64, 167.52, 165.49, 164.23, 161.16, 160.72, 158.60, 153.12, 152.01, 150.62, 142.98, 140.27, 139.82, 125.97, 122.79, 115.76, 108.86, 106.07, 96.38, 94.82, 93.56, 71.35, 60.65, 56.55, 56.50, 30.52, 28.97, 25.97, 21.24; HRMS calcd for $\text{C}_{34}\text{H}_{32}\text{N}_4\text{O}_9\text{S}$ $[\text{M} + \text{H}]^+$: 673.1963, found 673.1943.

Conclusions

In summary, aiming to develop novel and high-efficient agents with better biological activities, a series of pyrimidine-containing 4H-chromen-4-one derivatives were designed and synthesized. Antibacterial bioassays showed that most of compounds exhibited significant antibacterial activity against *Xac*, *Xoo* and *Rs*. Among them, the EC₅₀ values of compound **4c** against *Xac* and *Xoo* were 15.5 and 14.9 $\mu\text{g/mL}$ respectively, which were better than BT (51.7, 70.1%, respectively) and TC (77.9, 95.8%, respectively), compounds **4h** displayed appreciable activity against *Rs*, with the EC₅₀ values of 14.7 $\mu\text{g/mL}$, the result superior to BT (and 52.8 $\mu\text{g/mL}$) and TC (72.1 $\mu\text{g/mL}$). Compound **4c** demonstrated excellent curative activity and protection activity against bacterial blight of rice with the percentage inhibition of 42.4 and 49.2%, respectively, which were better than BT (35.2, 39.1%, respectively) and TC (30.8, 27.3%, respectively). Furthermore, the mechanism of compound **4c** against *Xoo* was confirmed by scanning electron microscope, the results showed that the compound destroyed the cell membrane structure of the bacteria, and the damage of the cell membrane was more serious as the concentration increased. These results indicated that the pyrimidine-containing 4H-chromen-4-one derivatives possess better antibacterial activities and could be further studied as potential replacement templates in the search for novel antibacterial agents.

Declarations

Ethics approval and consent to participate

This section are not applicable for this manuscript.

Consent for publication

This section are not applicable for this manuscript.

Availability of data and material

We have presented all our main data in the form of tables and figures. Meanwhile, all the copies of ^1H NMR, ^{13}C NMR, ^{19}F NMR and HRMS for the title compounds were presented in the Support Information. The datasets supporting the conclusions of the article are included within the article and the Support Information.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

This study is an outcome of constructive discussion with W Xue. SJ Su, M Chen carry out their synthesis and characterization experiments and carried out the ^1H NMR, ^{13}C NMR, ^{19}F NMR and HRMS spectral analyses, XM Tang and F Peng performed the antibacterial activity; TT Liu, Q Zhou, H Luo and M He assists in scanning electron microscope; SJ Su, M Chen were involved in the drafting of the manuscript and revising the manuscript. All authors read and approved the final manuscript.

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Figures

Figure 1

Structure of myricetin

Figure 2

Design strategy for target molecules

Figure 3

Crystalline structure of compound 4g

Curative activity

Protection activity

Figure 4
Curative and protective effects of compound 4g on the bacterial leaf blight of rice

Figure 5

SEM images for Xoo after incubated in different concentration of compound 4c

Figure 6

Synthetic route to title compounds 4a-4x

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