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ORIGINAL ARTICLE

Design, synthesis and fungicidal evaluation of novel psoralen derivatives containing sulfonohydrazide or acylthiourea moiety

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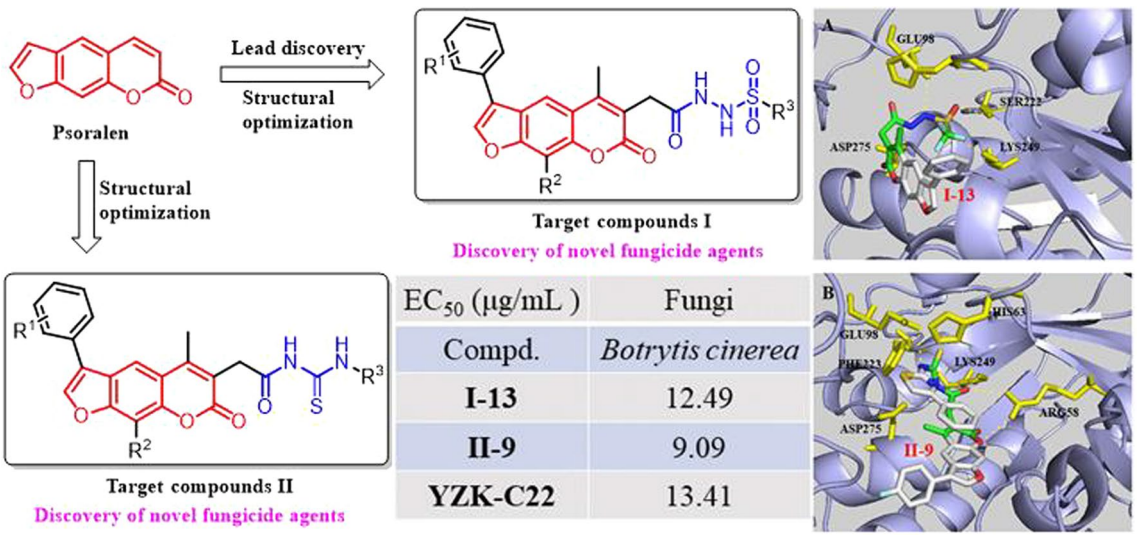
Abstract

To search a novel lead structure for antiphytopathogenic fungus agent, a series of novel psoralen derivatives possessing sulfonohydrazide or acylthiourea structure were designed and synthesized, and their fungicidal activity against seven phytopathogens was evaluated. Their structures were confirmed by melting points, ^{1}H NMR, ^{13}C NMR and HRMS, and the typical crystal structure was determined by X-ray diffraction for validation. Preliminary fungicidal activity showed that some of the title compounds exhibited certain-to-high fungicidal activity. Compound **I-13** exhibited good fungicidal activity against *Botrytis cinerea*, *Cercospora arachidicola* and *Physalospora piricola* with EC_{50} values of 12.49, 13.22 and 12.12 μg/mL, respectively. Compounds **II-9** and **II-15** showed over 90% inhibition against *B. cinerea* at 50 μg/mL in vitro. In particular, **II-9** exhibited significant higher fungicidal activity with a lower EC_{50} value of 9.09 μg/mL than the positive control YZK-C22 (13.41 μg/mL). Our studies found that sulfonohydrazide or acylthiourea-containing psoralen derivatives were promising fungicide leads deserve for further study.

Graphical abstract



Keywords Psoralen · Sulfonohydrazide · Acylthiourea · Antifungal activity · Molecular docking

Introduction

Plant diseases caused by fungi have caused severe losses to agriculture in the world every year, even emerged threat to human health and global food security [1–4]. It is well

Extended author information available on the last page of the article

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known that agrochemical application is one of a key measure for reducing crops loss caused by plant diseases in modern agriculture [5, 6]. However, the frequent application of traditional fungicides has brought a series of risks, such as environment pollution, resistance and so on [7, 8]. To tackle these serious problems, it is necessary to develop novel fungicides with high activities, low residue, low toxicity and novel modes of action.

Natural product-based lead derivation has become one of the hotspots of drugs and agrochemicals development in recent years because of their low toxicity, specific targets and easy degradation [9–12]. Furanocoumarins are an important class of fused heterocyclic compounds (Fig. 1), which existed in a large number of natural products, of which most showed strong biological activity, especially pharmacological activity [13–15]. Psoralen, a typical furanocoumarin, is an important plant-derived drug intermediate; the unique chemical structure makes it have a wide range of biological activities [16–18]. However, its application in preventing plant disease is rarely reported so far. Sulfonyl hydrazine derivatives (Fig. 2A–C) have a wide range of biological activities, such as antifungal [19], antitumor [20], antioxidant [21], antiviral activity [22] and so on. Moreover, the nitrogen atom of sulfonyl hydrazine as an electron-rich group can form hydrogen bonds with various residues of enzymes in organisms. Also, acylthiourea derivatives (Fig. 2D–F) have a wide range of biological activities, such as antitumor [23], antifungal [24], antiviral [25] and herbicidal activity [26].

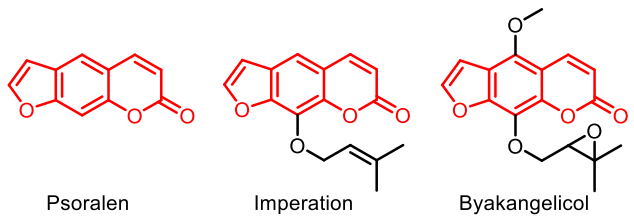


Fig. 1 Structures of psoralen, imperation and byakangelicol

It is known that pyruvate kinase has four subtypes (PKM1, PKM2, PKL and PKR) in mammals, which are often used in the research of anti-cancer drugs [27–29]. Our group discovered that pyruvate kinase was a potential fungicidal target [30, 31]. Subsequently, a series of novel isothiazole-purines targeting PK with good fungicidal activity were synthesized in our previous studies [32]. To continue the fungicidal development based on this target, according to computer aided drug design (CADD) and homology modeling, here, a series of novel psoralen derivatives containing sulfonylhydrazine or acylthiourea structure (Fig. 3) were rationally designed and synthesized, and they showed good affinity in docking simulation (Tables S1 and S2). Their fungicidal activity and structure–activity relationships (SARs) were studied. Moreover, the best active compounds were chosen for further validated by molecular docking simulation.

Results and discussion

Chemistry

The synthetic routes of the title compounds **I** and **II** are shown in Schemes 1, 2 and 3. The starting materials **1** were treated with dimethyl acetylsuccinate **2** in the presence of sulfuric acid 98% to give the intermediates **3**. Compounds **3** was treated with the corresponding α-haloaryl ketone **4** in the presence of potassium carbonate and potassium iodide in anhydrous acetonitrile to give compounds **5**. The intermediates **6** were obtained by reactions of compounds **5** and sodium hydroxide solution (1 mol/L) with propan-2-ol as the solvent, which further reacted with oxalyl chloride in dichloromethane to afford intermediates **8**. The key intermediates **9** were synthesized

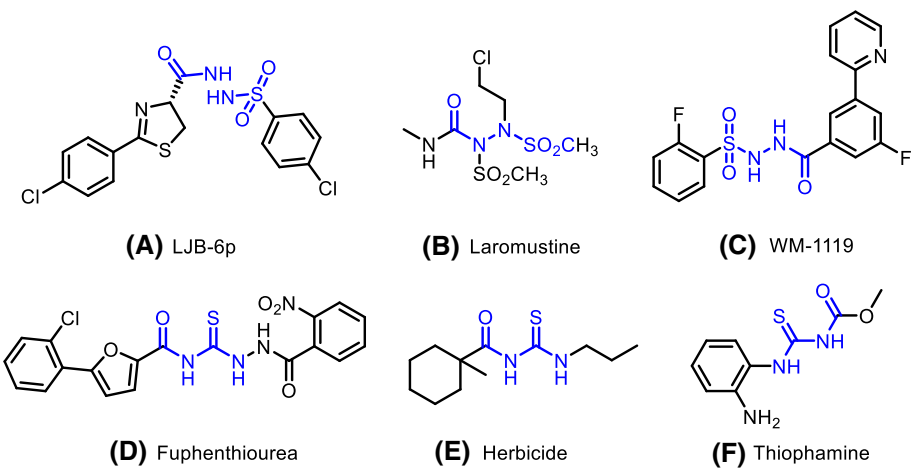


Fig. 2 Representative drugs and pesticides containing sulfonohydrazide or acylthiourea moiety

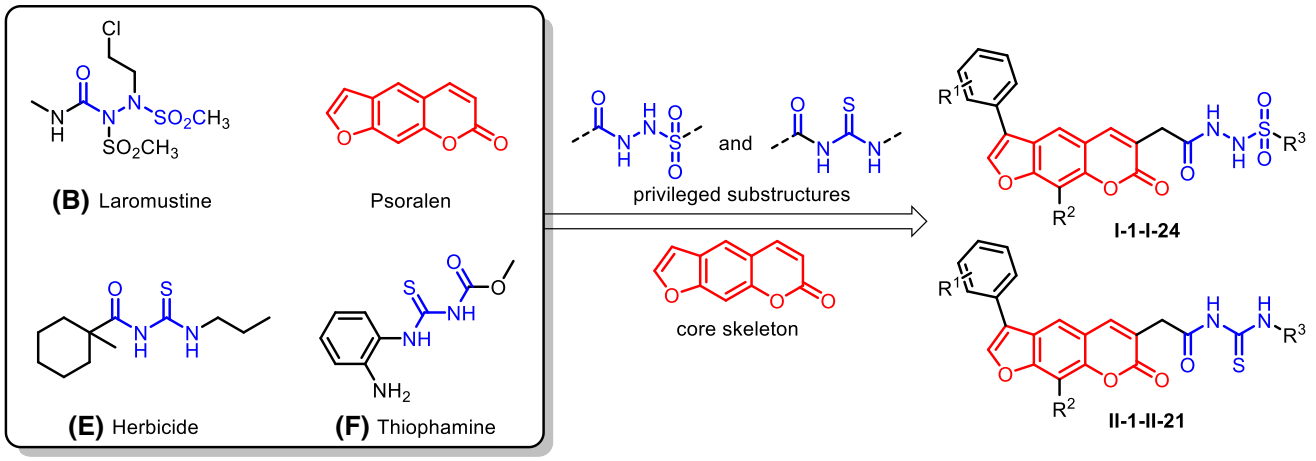
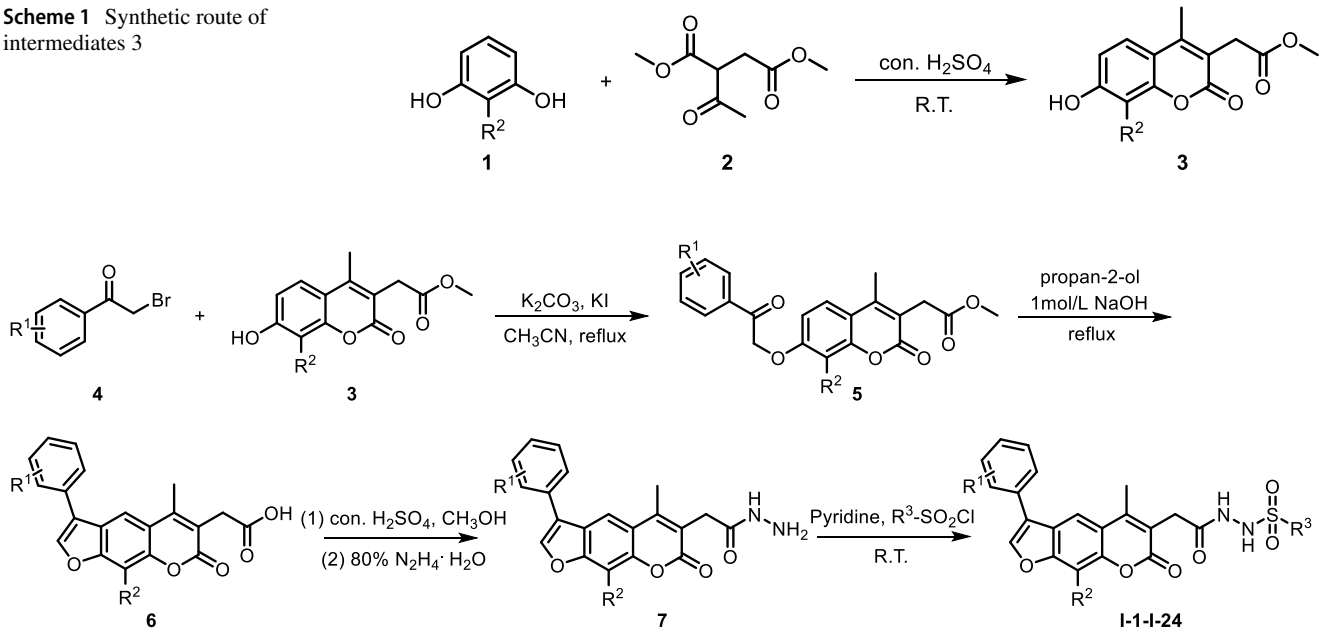


Fig. 3 Design of the target compounds **I** and **II**

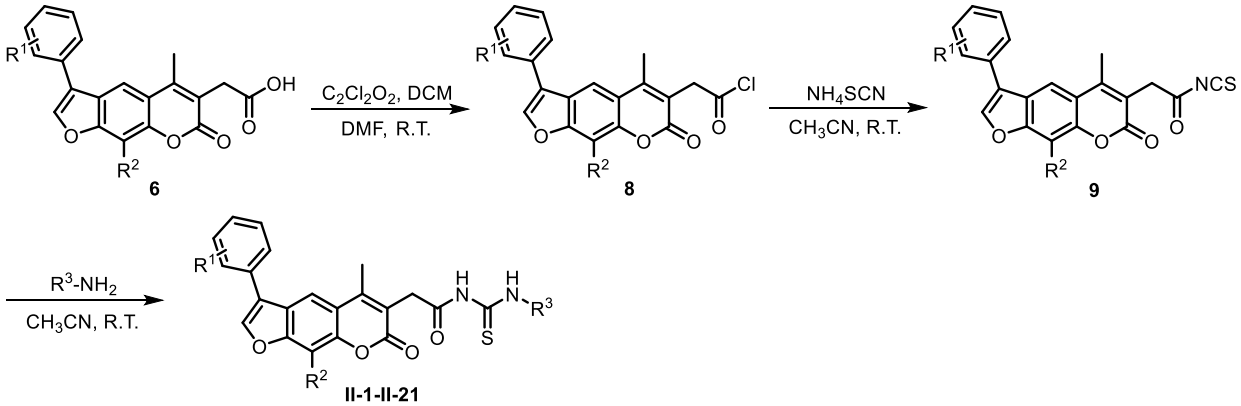
Scheme 1 Synthetic route of intermediates 3



I-1: R^1=4-Cl, R^2=H, R^3=2,4-dichlorophenyl;
I-2: R^1=H, R^2=H, R^3=cyclopropyl;
I-3: R^1=H, R^2=H, R^3=4-methoxyphenyl;
I-4: R^1=H, R^2=H, R^3=5-chloro-2,4-difluorophenyl;
I-5: R^1=H, R^2=H, R^3=phenyl;
I-6: R^1=4-F, R^2=H, R^3=4-methoxyphenyl;
I-7: R^1=H, R^2=H, R^3=CH_3;
I-8: R^1=4-Cl, R^2=H, R^3=4-methoxyphenyl;
I-9: R^1=4-F, R^2=H, R^3=4-bromophenyl;
I-10: R^1=H, R^2=CH_3, R^3=4-iodophenyl;
I-11: R^1=H, R^2=H, R^3=3,4-difluorophenyl;
I-12: R^1=H, R^2=H, R^3=2-naphthyl;
I-13: R^1=H, R^2=H, R^3=CF_3;
I-14: R^1=4-F, R^2=H, R^3=phenyl;
I-15: R^1=H, R^2=CH_3, R^3=CH_3;
I-16: R^1=H, R^2=H, R^3=4-iodophenyl;
I-17: R^1=H, R^2=H, R^3=2,4-dichlorophenyl;
I-18: R^1=H, R^2=H, R^3=3-pyridyl;
I-19: R^1=H, R^2=H, R^3=2-trifluoromethoxyphenyl;
I-20: R^1=H, R^2=H, R^3=3-methylphenyl;
I-21: R^1=H, R^2=H, R^3=4-methylphenyl;
I-22: R^1=H, R^2=H, R^3=4-cyanophenyl;
I-23: R^1=H, R^2=H, R^3=4-trifluoromethylphenyl;
I-24: R^1=4-Cl, R^2=H, R^3=4-tert-butylphenyl

Scheme 2 Synthetic route of the title compounds **I**

through reaction between corresponding **8** and ammonium thiocyanate in the presence of anhydrous acetonitrile. The key intermediates **7** were synthesized by esterification and hydrazinolysis reaction from the compounds **6**. Target compounds **I** were synthesized by reactions of compounds **7** and different sulfonyl chloride with anhydrous pyridine as the solvent and had favorable yields. Target compounds **II** were synthesized by reactions of compounds **9** and different amine with anhydrous acetonitrile as the solvent and had favorable yields.



II-1: R^1=H, R^2=H, R^3=3-methylphenyl; **II-2**: R^1=H, R^2=H, R^3=2,4-dichlorophenyl; **II-3**: R^1=H, R^2=H, R^3=4-fluorophenyl; **II-4**: R^1=H, R^2=H, R^3=2,2-difluoroethyl; **II-5**: R^1=4-F, R^2=H, R^3=2-bromophenyl; **II-6**: R^1=4-Cl. R^2=H, R^3=4-phenyl-1-butyl; **II-7**: R^1=4-Cl, R^2=H, R^3=3-methoxyphenyl; **II-8**: R^1=4-F, R^2=H, R^3=cyclopropyl; **II-9**: R^1=4-F, R^2=H, R^3=4-phenylthiazol-2-yl; **II-10**: R^1=4-F, R^2=H, R^3=3-hydroxy-1-propyl; **II-11**: R^1=4-F, R^2=H, R^3=4-morpholinophenyl; **II-12**: R^1=4-CH_3, R^2=H, R^3=4-chlorophenethyl; **II-13**: R^1=4-CH_3, R^2=H, R^3=3-fluorophenyl; **II-14**: R^1=4-F, R^2=H, R^3=2-chloro-3-pyridyl; **II-15**: R^1=4-F, R^2=H, R^3=4-(4-methylphenyl)thiazol-2-yl; **II-16**: R^1=4-F, R^2=H, R^3=3,5-dichlorophenyl; **II-17**: R^1=H, R^2=CH_3, R^3=3-nitrophenyl; **II-18**: R^1=4-Cl, R^2=H, R^3=2,4-dimethylphenyl; **II-19**: R^1=H, R^2=H, R^3=2-chlorophenethyl; **II-20**: R^1=H, R^2=H, R^3=2-hydroxyethyl; **II-21**: R^1=4-Cl, R^2=H, R^3=3-picolinyl

Scheme 3 Synthetic route of the title compounds **II**

Antifungal activity and SARs

The in vitro antifungal activity of the title compounds **I** and **II** against seven phytopathogens at 50 μg/mL are listed in Tables 1 and 2. For the series of target compounds **I**, some of compounds displayed obvious fungicidal activity against *Alternaria solani*, *Botrytis cinerea*, *Cercospora arachidicola* and *Physalospora piricola* at 50 μg/mL. Compounds **I-2**, **I-4**, **I-7**, **I-9**, **I-11** and **I-19** showed higher than 60% inhibition against *A. solani*, and more effective than the positive controls psoralen (56%) and YZK-C22 (58%) at the concentration of 50 μg/mL. Furthermore, compounds **I-13**, **I-14**, **I-16**, **I-18** and **I-24** exhibited good fungicidal activity against *C. arachidicola*. It was worthy to note that compound **I-13** exhibited excellent fungicidal activities against *B. cinerea*, *C. arachidicola* and *P. piricola* at 50 μg/mL in vitro with 67%, 72% and 63% inhibition rates, respectively. The bioassay results indicated that the general sequence of the effect of group R^1 in the benzene (**I-3**, **I-6** and **I-8**) on antifungal activity was 4-F > 4-Cl > H. The bioactivities of compounds **I-10** and **I-15** declined in comparison with the corresponding compounds **I-7** and **I-16** (**I-7** vs **I-15**, **I-10** vs **I-16**), and it was speculated that the sequence of the fungicidal activity of these compounds with R^2 was H > CH_3. Moreover, compounds **I-3**, **I-5**, **I-9**, **I-14**, **I-17**, **I-19**, **I-21**, **I-23** and **I-24** had similar activities, and it was speculated that electronic effects of different groups in the benzene at group R^3 site had little influence on the fungicidal activity. For the series of target compounds **II**, some of compounds exhibited certain-to-high fungicidal activity at 50 μg/mL. Several compounds exhibited excellent in vitro fungicidal activity against *A. solani*, *B. cinerea*, *G. zeae* and *P. piricola* at 50 μg/mL. Furthermore, compounds **II-8**, **II-9**, **II-12**, **II-15**, **II-16** and **II-20** showed over 60% inhibition against *B. cinerea*, and they are more effective than the positive control psoralen at the concentration of 50 μg/mL. In particular, compounds **II-9** and **II-15** exhibited outstanding activity (> 90%). It was also worthy to note that compound **II-7** exhibited excellent in vitro fungicidal activity against *A. solani*, *G. zeae* and *P. piricola* at 50 μg/mL with 82%, 71% and 78% inhibition rates, respectively. On the whole, compounds with aryl group substitution (**II-1**-**II-3**, **II-5**, **II-7** and **II-16**-**II-18**) at R^3 site showed better antifungal activity than alkyl substitute compounds (**II-4**, **II-8** and **II-10**). Meanwhile, compounds with the group 4-arylthiazol-2-amine moiety (**II-9** and **II-15**) at R^3 site displayed excellent fungicidal activity against *B. cinerea*.

Median effective concentration (EC_{50}) values of several compounds with superior in vitro fungicidal activity were further tested, and the results are shown in Tables 3 and 4. For the series of target compounds **I**, as can be seen, compound **I-13** exhibited good antifungal activity against *B. cinerea*, *C. arachidicola* and *P. piricola* with an EC_{50} value of 12.49, 13.22 and 12.12 μg/mL, respectively. Compounds **I-2**, **I-4**, **I-7**, **I-9**, **I-11** and **I-19** exhibited good fungicidal activity against *A. solani*, of which **I-4** and **I-7** displayed strong inhibition of the growth of *A. solani* with the EC_{50} value of 11.35 μg/mL and 13.42 μg/mL, respectively. Compound **I-7** not only effective against *A. solani* but also *B. cinerea*, with an EC_{50} value of 25.43 μg/mL. Compounds

Table 1 In vitro fungicidal activity of target compounds I against phytopathogens

Compd	Mycelium growth inhibitory rate (%) at 50 μg/mL						
	A. s[a]	*B. c*	*C. a*	*G. z*	*P. p*	*P. s*	*S. s*
I-1	32 ± 2	24 ± 1	14 ± 1	23 ± 1	24 ± 1	23 ± 1	23 ± 1
I-2	62 ± 2	25 ± 0	42 ± 1	24 ± 1	31 ± 1	23 ± 1	25 ± 1
I-3	28 ± 2	39 ± 1	42 ± 1	27 ± 1	25 ± 1	15 ± 2	24 ± 1
I-4	71 ± 2	38 ± 2	40 ± 1	28 ± 1	35 ± 1	25 ± 1	16 ± 1
I-5	36 ± 3	41 ± 1	42 ± 1	27 ± 1	25 ± 1	22 ± 1	18 ± 1
I-6	47 ± 3	38 ± 2	40 ± 1	41 ± 1	26 ± 1	21 ± 0	23 ± 0
I-7	68 ± 2	61 ± 1	31 ± 1	26 ± 2	33 ± 1	38 ± 1	24 ± 1
I-8	38 ± 2	24 ± 1	44 ± 1	23 ± 1	20 ± 1	23 ± 0	25 ± 1
I-9	60 ± 2	26 ± 1	27 ± 1	22 ± 1	16 ± 1	19 ± 2	27 ± 1
I-10	9 ± 0	33 ± 0	25 ± 1	32 ± 0	5 ± 0	4 ± 1	19 ± 0
I-11	70 ± 0	42 ± 0	44 ± 1	39 ± 1	27 ± 1	24 ± 2	20 ± 1
I-12	57 ± 2	24 ± 1	35 ± 1	32 ± 1	22 ± 1	24 ± 1	28 ± 1
I-13	41 ± 2	67 ± 1	72 ± 1	34 ± 1	63 ± 1	23 ± 1	31 ± 1
I-14	52 ± 0	27 ± 0	66 ± 0	39 ± 1	26 ± 2	14 ± 1	23 ± 1
I-15	20 ± 1	37 ± 1	27 ± 0	30 ± 1	12 ± 0	7 ± 1	14 ± 0
I-16	27 ± 0	31 ± 1	77 ± 1	23 ± 1	26 ± 2	18 ± 1	27 ± 1
I-17	38 ± 2	34 ± 0	41 ± 1	24 ± 2	26 ± 2	25 ± 1	25 ± 1
I-18	32 ± 2	37 ± 1	64 ± 0	23 ± 1	67 ± 1	21 ± 0	30 ± 2
I-19	65 ± 2	21 ± 1	33 ± 1	30 ± 1	38 ± 0	26 ± 2	24 ± 1
I-20	33 ± 0	29 ± 2	39 ± 1	23 ± 1	22 ± 1	30 ± 1	24 ± 1
I-21	42 ± 3	43 ± 1	43 ± 0	40 ± 2	31 ± 1	14 ± 1	29 ± 1
I-22	36 ± 3	41 ± 1	42 ± 1	27 ± 1	25 ± 1	22 ± 1	18 ± 1
I-23	33 ± 0	24 ± 1	33 ± 1	22 ± 1	21 ± 1	38 ± 2	28 ± 1
I-24	37 ± 2	26 ± 1	63 ± 1	29 ± 1	18 ± 1	27 ± 1	28 ± 1
Psoralen	56 ± 1	50 ± 1	65 ± 1	63 ± 1	44 ± 1	52 ± 0	58 ± 1
YZK-C22[b]	58 ± 1	72 ± 1	74 ± 1	75 ± 1	57 ± 1	81 ± 1	61 ± 1

[a]*A. s*: *Alternaria solani*, *B. c*: *Botrytis cinerea*, *C. a*: *Cercospora arachidicola*, *G. z*: *Gibberella zeae*, *P. p*: *Physalospora piricola*, *P. s*: *Pellicularia sasakii*, *S. s*: *Sclerotinia sclerotiorum*

[b]3-(4-methyl-1,2,3-thiadiazol-5-yl)-6-(trichloromethyl)-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazole

I-14, **I-16**, **I-18** and **I-24** exhibited good fungicidal activity against *C. arachidicola*, of which **I-16** displayed strong inhibition of the growth of *C. arachidicola* with an EC_{50} value of 9.73 μg/mL, and it was more active than the positive control psoralen with a corresponding EC_{50} value of 23.76 μg/mL. For the series of target compounds **II**, the results indicated that compound **II-7** exhibited good antifungal activity against *A. solani*, *G. zeae* and *P. piricola* with EC_{50} values of 15.26, 27.26 and 19.16 μg/mL, respectively. Compounds **II-8**, **II-9**, **II-12**, **II-15**, **II-16** and **II-20** exhibited good fungicidal activity against *B. cinerea*, of which **II-9** and **II-15** displayed strong inhibition of the growth of *B. cinerea*, with an EC_{50} value of 9.09 μg/mL and 10.09 μg/mL, respectively. Compound **II-15** is not only effective against *B. cinerea* but also *C. arachidicola*, with an EC_{50} value of 31.19 μg/mL. Compound **II-9** with 4-phenylthiazole-2-amine substitution at the R^3 site was the most effective compound against *B. cinerea* and could be used as an antifungal lead for further optimization.

Molecular docking analysis

In order to validate the possible mode of action of target compounds and further explain the SARs, the docking analysis of selected compounds (**I-13** and **II-9**), psoralen and YZK-C22 was performed with pyruvate kinase of *B. cinerea* (BcPK). As shown in Fig. 4, compound **I-13** formed four hydrogen bonds with the residues GLU98, ASP275, SER222 and LYS249, respectively. And the benzene ring of **I-13** formed a π-π stacking interaction with the residue HIS63. Compound **II-9** formed five hydrogen bonds with the amino acid residues ARG58 (3.05 and 3.15 Å), GLU98, ASP275 and LYS249, respectively, and also formed two π-π stacking interactions with the residues HIS63 and PHE223, respectively. While the positive controls psoralen and YZK-C22 only formed two hydrogen bonds with the amino acid residues ASN60, HIS69 (for psoralen), and ASN60, LYS249 (for YZK-C22), respectively. These results indicated that the

Table 2 In vitro fungicidal activity of target compounds **II** against phytopathogens

Compd	Mycelium growth inhibitory rate (%) at 50 μg/mL						
	A. s	*B. c*	*C. a*	*G. z*	*P. p*	*P. s*	*S. s*
II-1	13 ± 0	29 ± 0	26 ± 1	33 ± 1	7 ± 0	21 ± 1	9 ± 2
II-2	0	39 ± 1	30 ± 1	24 ± 1	18 ± 1	8 ± 1	12 ± 0
II-3	43 ± 1	44 ± 1	27 ± 0	41 ± 1	19 ± 1	1 ± 1	16 ± 2
II-4	7 ± 0	44 ± 1	24 ± 0	16 ± 1	6 ± 1	12 ± 1	9 ± 1
II-5	18 ± 1	37 ± 1	30 ± 1	19 ± 0	10 ± 0	8 ± 1	10 ± 1
II-6	4 ± 0	35 ± 1	27 ± 0	16 ± 1	11 ± 1	17 ± 0	11 ± 1
II-7	82 ± 1	39 ± 1	23 ± 1	71 ± 1	78 ± 0	9 ± 0	9 ± 0
II-8	0	64 ± 0	24 ± 1	27 ± 1	8 ± 1	10 ± 1	16 ± 0
II-9	33 ± 0	100	33 ± 0	40 ± 1	33 ± 1	52 ± 0	16 ± 1
II-10	17 ± 0	52 ± 1	24 ± 1	33 ± 1	17 ± 0	12 ± 0	18 ± 1
II-11	9 ± 0	41 ± 1	23 ± 1	31 ± 1	14 ± 1	25 ± 1	11 ± 1
II-12	10 ± 1	69 ± 0	29 ± 0	30 ± 1	8 ± 1	15 ± 1	17 ± 1
II-13	12 ± 1	49 ± 0	27 ± 1	33 ± 1	19 ± 1	19 ± 1	19 ± 2
II-14	0	33 ± 1	26 ± 1	24 ± 1	19 ± 1	4 ± 1	10 ± 1
II-15	16 ± 1	92 ± 1	61 ± 1	36 ± 0	17 ± 0	4 ± 1	19 ± 2
II-16	0	66 ± 1	14 ± 1	25 ± 1	7 ± 0	10 ± 1	5 ± 1
II-17	9 ± 0	33 ± 1	24 ± 0	33 ± 1	12 ± 0	9 ± 2	6 ± 1
II-18	0	31 ± 0	21 ± 1	23 ± 0	15 ± 1	14 ± 2	12 ± 0
II-19	23 ± 1	44 ± 0	24 ± 0	22 ± 1	17 ± 0	13 ± 1	18 ± 1
II-20	7 ± 1	60 ± 0	39 ± 1	36 ± 0	20 ± 0	20 ± 0	11 ± 1
II-21	13 ± 0	49 ± 0	31 ± 0	33 ± 1	0	33 ± 1	13 ± 1
Psoralen	56 ± 1	50 ± 1	65 ± 1	63 ± 1	44 ± 1	52 ± 0	58 ± 1
YZK-C22	58 ± 1	72 ± 1	74 ± 1	75 ± 1	57 ± 1	81 ± 1	61 ± 1

Table 3 The in vitro antifungal EC_{50} of selected compounds **I**

Fungi	Compd	Regression equation	R^2	EC_{50} (μg/mL)
A. solani	**I-2**	$y = 1.8398 + 2.1715\,x$	0.9744	28.53
	I-4	$y = 3.0998 + 1.8010\,x$	0.9085	11.35
	I-7	$y = 3.1593 + 1.6323x$	0.9537	13.42
	I-9	$y = 3.1128 + 1.4142\,x$	0.9649	21.60
	I-11	$y = 2.1930 + 1.9878\,x$	0.9903	25.83
	I-19	$y = 2.5881 + 1.6825\,x$	0.9935	27.13
B. cinerea	**I-7**	$y = 3.3449 + 1.1777\,x$	0.9807	25.43
	I-13	$y = 3.1912 + 1.6498\,x$	0.9227	12.49
	YZK-C22 [32]	$y = 2.9305 + 1.8358\,x$	0.9630	13.41
C. arachidicola	**I-13**	$y = 2.7800 + 1.9802\,x$	0.9549	13.22
	I-14	$y = 2.2460 + 1.8463\,x$	0.9941	31.02
	I-16	$y = 3.5285 + 1.4890\,x$	0.9745	9.73
	I-18	$y = 1.8529 + 2.0150\,x$	0.9933	36.46
	I-24	$y = 2.5223 + 1.6741\,x$	0.9975	30.20
	Psoralen	$y = 1.6622 + 2.4260\,x$	0.9308	23.76
P. piricola	**I-13**	$y = 3.1335 + 1.7227\,x$	0.9175	12.12
	I-18	$y = 3.4516 + 1.4457\,x$	0.9433	11.78

Table 4 The in vitro antifungal EC_{50} of selected compounds **II**

Fungi	Compd	Regression equation	R^2	EC_{50} (μg/mL)
A. solani	**II-7**	$y = 2.0607 + 2.4837\,x$	0.9856	15.26
B. cinerea	**II-8**	$y = 2.1437 + 1.9580\,x$	0.9878	28.76
	II-9	$y = 3.2680 + 1.8065\,x$	0.9751	9.09
	II-12	$y = 1.8766 + 2.0810\,x$	0.9702	31.69
	II-15	$y = 2.8630 + 2.1287\,x$	0.9813	10.09
	II-16	$y = 2.4977 + 1.7962\,x$	0.9629	24.72
	II-20	$y = 2.1781 + 1.8040\,x$	0.9970	36.66
	YZK-C22 [32]	$y = 2.9305 + 1.8358\,x$	0.9630	13.41
C. arachidicola	**II-15**	$y = 1.9735 + 2.0257\,x$	0.9861	31.19
	Psoralen	$y = 1.6622 + 2.4260\,x$	0.9308	23.76
G. zeae	**II-7**	$y = 1.9772 + 2.1058\,x$	0.9924	27.26
	Psoralen	$y = 3.2638 + 1.1991\,x$	0.9832	28.05
	YZK-C22 [32]	$y = 3.6197 + 1.7184\,x$	0.9972	6.36
P. piricola	**II-7**	$y = 2.0835 + 2.2743\,x$	0.9799	19.16

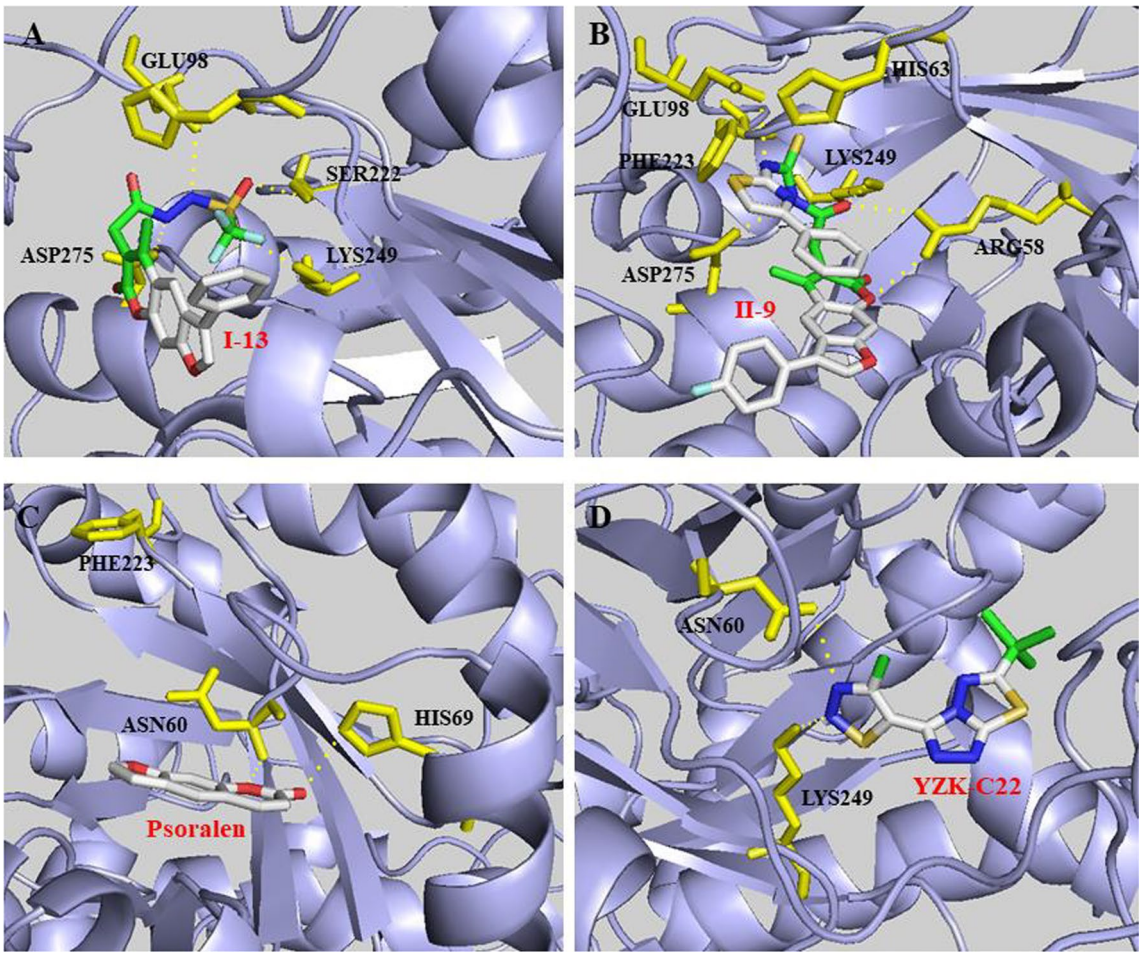


Fig. 4 Docking modes of **I-13** (A), **II-9** (B), Psoralen (C) and YZK-C22 (D) with *B. cinerea* PK

target compounds possessed strong interaction with BcPK, exhibited good fungicidal activity.

It is well known that pyruvate kinase widely exists in animals, plants, microorganisms and culture cells. To further explore the selective toxicity of the target compounds with good fungicidal activity, the binding energy difference of compounds **I-13** or **II-9** between pyruvate kinase of *Homo sapiens* (HsPK) and BcPK was calculated by molecular docking comparison (Table S3). The docking results showed that the binding energy between **I-13** or **II-9** and BcPK was − 9.3 or − 8.1 kcal/mol, respectively, which was slightly higher than that between **I-13** or **II-9** and HsPK, with a corresponding binding energy of − 9.2 or − 7.9 kcal/mol, respectively. These results revealed that the designed compounds had a certain degree of selective toxicity in fungi and mammals.

Conclusions

A series of novel psoralen derivatives containing sulfonohydrazide or acylthiourea structure were rationally designed, synthesized, and their fungicidal activity was evaluated. The preliminary bioactivity showed that most of the target compounds possessed a certain degree of in vitro fungicidal activity at a concentration of 50 μg/mL. Particularly, compounds **I-13** and **II-9** exhibited excellent fungicidal activity against *B. cinerea* with an EC_{50} value of 12.49 μg/mL and 9.09 μg/mL, respectively. Furthermore, molecular docking results showed that **I-13** and **II-9** can be well docked into the active site of the enzyme *B. cinerea* PK. These results demonstrate that psoralen derivatives bearing sulfonohydrazide or acylthiourea could be novel fungicide lead compounds for further studies.

Experimental

Instruments and reagents

^{1}H NMR and ^{13}C NMR spectra were obtained on a Bruker AV400 spectrometer (400 Hz) with tetramethylsilane (TMS) as the internal standard and DMSO-d_6 as solvent. Chemical shift values (δ) were reported in ppm, and coupling constants (J) were reported in Hz. Melting points were obtained using an X-4 binocular microscope melting point apparatus and were uncorrected. High-resolution mass spectra (HRMS) data were obtained on an Agilent 6520 Q-TOF LC/MS instrument (California, United States). Crystal structure was collected on a Rigaku 007 Saturn 70 diffractometer (Rigaku, Tokyo, Japan). Column chromatography purification was performed with silica gel (100–200 mesh, Qingdao, China). Reagents were all analytically or chemically pure and used as received. The intermediates **3**, **5** and **6** were synthesized according to the literature [33] with some modifications.

General synthetic procedure for target compounds I

To a solution of the intermediates **7** (0.29 mmol) in pyridine (10 mL), the corresponding sulfonyl chloride (0.29 mmol) was added. Then, the mixture was stirred at room temperature for 12 h. After the reaction was completed (checked by TLC), 30 mL of water was added and then extracted with ethyl acetate (3 × 15 mL), the organic layer was combined and washed with dilute hydrogen chloride (1 mol/L, 2 × 20 mL) and brine (3 × 10 mL), dried with anhydrous sodium sulfate, and then concentrated in vacuum. The residue was purified by column chromatography on silica gel using dichloromethane/methanol (v/v, 20:1) as eluent to give the target compounds **I**.

Data for 2,4-dichloro-*N*'-(2-(3-(4-chlorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-1**): White solid; Yield, 81%; m.p. 136–137 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.30 (*s*, 1H, CO–NH–N<u>H</u>–SO_2), 10.17 (*s*, 1H, CO–N<u>H</u>–NH–SO_2), 8.46 (s, 1H, Ar–C=C<u>H</u>–O), 8.06 (s, 1H, Ar–<u>H</u>), 7.94 (*d*, J = 8.5 Hz, 1H, Ar–<u>H</u>), 7.80 (*d*, J = 8.0 Hz, 2H, Ar–<u>H</u>), 7.73 (d, J = 12.4 Hz, 2H, Ar–<u>H</u>), 7.57 (*d*, J = 8.1 Hz, 2H, Ar–<u>H</u>), 7.47 (d, J = 8.3 Hz, 1H, Ar–<u>H</u>), 3.44 (*s*, 2H, C<u>H</u>$_2$–CONH), 2.33 (*s*, 3H, C=C–C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.76 (s), 160.94 (s), 156.46 (s), 150.40 (s), 150.20 (s), 145.14 (s), 138.68 (s), 136.28 (s), 133.87 (s), 133.17 (s), 132.84 (s), 131.50 (s), 130.02 (s), 129.60 (s), 129.37 (s), 127.59 (s), 122.97 (s), 120.63 (s), 118.19 (s), 117.30 (s), 116.91 (s), 99.97 (s), 32.27 (s), 16.05 (s). HRMS (ESI) m/z: calcd. for $C_{26}H_{17}NaCl_3N_2O_6S$ ($[M + Na]^+$) 612.9765, found 612.9763.

Data for *N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)cyclopropanesulfonohydrazide (**I-2**): White solid; Yield, 74%; m.p. 224–225 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (*d*, J = 2.9 Hz, 1H, CO–NH–N<u>H</u>–SO_2), 9.46 (*d*, J = 3.0 Hz, 1H, CO–N<u>H</u>–NH–SO_2), 8.48 (*s*, 1H, Ph-C=C<u>H</u>–O), 8.20 (*s*, 1H, Ar–<u>H</u>), 7.84–7.79 (m, 3H, Ar–<u>H</u>), 7.55 (t, J = 7.6 Hz, 2H, Ar–<u>H</u>), 7.43 (t, J = 7.4 Hz,1H, Ar–<u>H</u>), 3.62 (s, 2H, C<u>H</u>$_2$-CONH), 2.54 (s, 3H, C=C–C<u>H</u>$_3$), 2.47–2.41 (m, 1H, SO_2-C<u>H</u>$(CH_2)_2$), 1.01–0.78 (m, 4H, CH(C<u>H</u>$_2)_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.55 (s), 160.72 (s), 156.03 (s), 149.95 (s), 144.36 (s), 130.65 (s), 129.20 (s), 127.82 (s), 127.22 (s), 122.83 (s), 121.27 (s), 117.97 (s), 117.02 (s), 116.67 (s), 99.53 (s), 32.00 (s), 29.31 (s), 15.76 (s), 5.13 (s). HRMS (ESI) m/z: calcd. for $C_{23}H_{20}NaN_2O_6S$ ($[M + Na]^+$) 475.0934, found 475.0930.

Data for 4-methoxy-*N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-3**): White solid; Yield, 74%; m.p. 222–223 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (d,

$J = 3.2$ Hz, 1H, CO–NH–N<u>H</u>–SO_2), 9.69 (d, $J = 3.3$ Hz, 1H, CO–N<u>H</u>–NH–SO_2), 8.48 (s, 1H, Ph-C=C<u>H</u>–O), 8.16 (s, 1H, Ar–<u>H</u>), 7.84–7.79 (m, 3H, Ar–<u>H</u>), 7.72 (d, $J = 8.7$ Hz, 2H, Ar–<u>H</u>), 7.55 (t, $J = 7.6$ Hz, 2H, Ar–<u>H</u>), 7.44 (t, $J = 7.4$ Hz, 1H, Ar–<u>H</u>), 6.99 (d, $J = 8.8$ Hz, 2H, Ar–<u>H</u>), 3.73 (s, 3H, Ph-OC<u>H</u>$_3$), 3.46 (s, 2H, C<u>H</u>$_2$–CONH), 2.37 (s, 3H, C=C–C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.57 (s), 162.76 (s), 160.59 (s), 156.03 (s), 149.94 (s), 149.83 (s), 144.49 (s), 130.71 (s), 130.19 (s), 129.91 (s), 129.21 (s), 127.84 (s), 127.22 (s), 123.11 (s), 117.85 (s), 116.88 (s), 116.58 (s), 113.88 (s), 99.51 (s), 55.45 (s), 32.38 (s), 15.63 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{23}N_2O_7S$ ($[M+H]^+$) 519.1220, found 519.1216.

Data for 5-chloro-2,4-difluoro-*N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-4**): White solid; Yield, 92%; m.p. 201–202 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.50 (d, $J = 2.1$ Hz, 1H, CO–NH–N<u>H</u>–SO_2), 10.42 (d, $J = 1.8$ Hz, 1H, CO–N<u>H</u>–NH–SO_2), 8.47 (s, 1H, Ph-C = C<u>H</u>–O), 8.14 (s, 1H, Ar–<u>H</u>), 7.90 (t, $J = 7.5$ Hz, 1H, Ar–<u>H</u>), 7.81 (d, $J = 7.3$ Hz, 2H, Ar–<u>H</u>), 7.78–7.73 (m, 2H, Ar–<u>H</u>), 7.55 (t, $J = 7.6$ Hz, 2H, Ar–<u>H</u>), 7.43 (t, $J = 7.4$ Hz, 1H,Ar–<u>H</u>), 3.47 (s, 2H, C<u>H</u>$_2$–CONH), 2.38 (s, 3H, C=C–C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.40 (s), 160.49 (s), 156.03 (s), 149.91 (s), 149.79 (s), 144.34 (s), 131.52 (s), 130.63 (s), 129.19 (s), 127.82 (s), 127.20 (s), 122.81 (s), 121.25 (s), 117.57 (s), 116.75 (s), 116.58 (s), 99.51 (s), 31.87 (s), 15.47 (s). HRMS (ESI) m/z: calcd. for $C_{26}H_{18}ClF_2N_2O_6S$ ($[M+H]^+$) 559.0537, found 559.0537.

Data for *N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-5**): White solid; Yield, 72%; m.p. 267–268 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.27 (s, 1H, CO–NH–N<u>H</u>–SO_2), 9.90 (s, 1H, CO–N<u>H</u>–NH–SO_2), 8.47 (s, 1H, Ph–C=C<u>H</u>–O), 8.16 (s, 1H, Ar–<u>H</u>), 7.81 (dd, $J = 10.2$, 4.3 Hz, 6H, Ar–<u>H</u>), 7.56 (dd, $J = 12.9$, 5.3 Hz, 2H, Ar–<u>H</u>), 7.50–7.42 (m, 3H, Ar–<u>H</u>), 3.47 (s, 2H, C<u>H</u>$_2$–CONH), 2.37 (s, 3H, C=C–C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.18 (s), 161.09 (s), 156.53 (s), 150.45 (s), 150.33 (s), 144.85 (s), 139.40 (s), 133.34 (s), 131.14 (s), 129.71 (s), 129.21 (s), 128.33 (s), 128.09 (s), 127.73 (s), 123.33 (s), 122.08 (s), 118.25 (s), 117.34 (s), 117.08 (s), 100.02 (s), 32.35 (s), 16.14 (s). HRMS (ESI) m/z: calcd. for $C_{26}H_{21}N_2O_6S$ ($[M+H]^+$) 489.1115, found 489.1114.

Data for *N*'-(2-(3-(4-fluorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)acetyl)-4-methoxybenzenesulfonohydrazide (**I-6**): White solid; Yield, 74%; m.p. 257–258 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.23 (s, 1H, CO–NH–N<u>H</u>–SO_2), 9.69 (s, 1H, CO–N<u>H</u>–NH–SO_2), 8.47 (s, 1H, Ar–C=C<u>H</u>–O), 8.13 (s, 1H, Ar–<u>H</u>), 7.89–7.85 (m, 2H, Ar–<u>H</u>), 7.80 (s, 1H, Ar–<u>H</u>), 7.71 (d, $J = 8.7$ Hz, 2H, Ar–<u>H</u>), 7.38 (t, $J = 8.6$ Hz, 2H, Ar–<u>H</u>), 6.98 (d, $J = 8.5$ Hz, 2H, Ar–<u>H</u>), 3.73 (s, 3H, Ph-OC<u>H</u>$_3$), 3.46 (s, 2H, C<u>H</u>$_2$-CONH), 2.37 (s, 3H, C=C–C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.57 (s), 162.52 (s), 161.08 (s), 155.95 (s), 149.97 (s), 149.85 (s), 144.61 (s), 130.22 (s), 129.90 (s), 129.34 (s), 129.26 (s), 122.74 (s), 120.35 (s), 117.99 (s), 117.02 (s), 116.53 (s), 116.20 (s), 115.98 (s), 113.87 (s), 99.51 (s), 55.45 (s), 32.46 (s), 15.64 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{22}FN_2O_7S$ ($[M+H]^+$) 537.1126, found 537.1126.

Data for *N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)methanesulfonohydrazide (**I-7**): White solid; Yield, 61%; m.p. 257–258 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (d, $J = 2.8$ Hz, 1H, CO–NH–N<u>H</u>–SO_2), 9.50 (d, $J = 2.9$ Hz, 1H, CO–N<u>H</u>–NH–SO_2), 8.48 (s, 1H, Ph-C=C<u>H</u>–O), 8.20 (s, 1H, Ar–<u>H</u>), 7.84–7.80 (m, 3H, Ar–<u>H</u>), 7.55 (t, $J = 7.6$ Hz, 2H, Ar–<u>H</u>), 7.44 (t, $J = 7.4$ Hz, 1H, Ar–<u>H</u>), 3.62 (s, 2H, C<u>H</u>$_2$–CONH), 2.91 (s, 3H, C<u>H</u>$_3$–SO_2NH), 2.54 (s, 3H, C=C–C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.87 (s), 160.74 (s), 156.02 (s), 149.95 (s), 149.92 (s), 144.36 (s), 130.64 (s), 129.20 (s), 127.83 (s), 127.22 (s), 122.85 (s), 121.27 (s), 118.06 (s), 116.88 (s), 116.71 (s), 99.54 (s), 39.68 (s), 32.22 (s), 15.71 (s). HRMS (ESI) m/z: calcd. for $C_{21}H_{19}N_2O_6S$ ($[M+H]^+$) 427.0958, found 427.0955.

Data for *N*'-(2-(3-(4-chlorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)acetyl)-4-methoxybenzenesulfonohydrazide (**I-8**): White solid; Yield, 54%; m.p. 272–273 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (s, 1H, CO–NH–N<u>H</u>–SO_2), 9.69 (s, 1H, CO–N<u>H</u>–NH–SO_2), 8.51 (s, 1H, Ar–C=C<u>H</u>–O), 8.13 (s, 1H, Ar–<u>H</u>), 7.82 (d, $J = 18.9$ Hz, 3H, Ar–<u>H</u>), 7.72 (d, $J = 6.6$ Hz, 2H, Ar–<u>H</u>), 7.60 (s, 2H, Ar–<u>H</u>), 6.98 (d, $J = 6.4$ Hz, 2H, Ar–<u>H</u>), 3.72 (s, 3H, Ph-OC<u>H</u>$_3$), 3.46 (s, 2H, C<u>H</u>$_2$-CONH), 2.37 (s, 3H, C=C–C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.57 (s), 162.52 (s), 160.55 (s), 156.34 (s), 150.00 (s), 149.79 (s), 144.74 (s), 132.36 (s), 130.25 (s), 129.89 (s), 129.61 (s), 129.16 (s), 128.97 (s), 122.74 (s), 120.19 (s), 117.88 (s), 116.92 (s), 116.56 (s), 113.87 (s), 99.54 (s), 55.44 (s), 31.85 (s), 15.63 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{22}ClN_2O_7S$ ($[M+H]^+$) 553.0831, found 553.0826.

Data for 4-bromo-*N*'-(2-(3-(4-fluorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-9**): White solid; Yield, 81%; m.p. 269–270 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H, CO–NH–N<u>H</u>–SO_2), 10.05 (s, 1H, CO–N<u>H</u>–NH–SO_2), 8.46 (s, 1H, Ar–C=C<u>H</u>–O), 8.13 (s, 1H, Ar–<u>H</u>), 7.89–7.84 (m, 2H, Ar–<u>H</u>), 7.80 (s, 1H, Ar–<u>H</u>), 7.73–7.67 (m, 4H, Ar–<u>H</u>), 7.38 (t, $J = 8.9$ Hz, 2H, Ar–<u>H</u>), 3.47 (s, 2H, C<u>H</u>$_2$-CONH), 2.38 (s, 3H, C=C–C<u>H</u>$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.84 (s), 160.56 (s), 155.97 (s), 149.93 (s), 149.88 (s), 144.35 (s), 138.16 (s), 131.78 (s), 129.68 (s), 129.33 (s), 129.25 (s), 126.80 (s), 122.76 (s), 120.34 (s), 117.75 (s), 116.84 (s), 116.53 (s), 116.20 (s), 115.99 (s), 99.53 (s), 31.89 (s), 15.62 (s). HRMS (ESI) m/z: calcd. for $C_{26}H_{19}BrFN_2O_6S$ ($[M+H]^+$) 585.0126, found 585.0124.

Data for *N*'-(2-(5,9-dimethyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)-4-iodobenzenesulfonohydrazide (**I-10**): Yellow solid; Yield, 73%; m.p. 276–277 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (s, 1H, CO–NH–NH–SO_2), 10.01 (s, 1H, CO–NH–NH–SO_2), 8.42 (s, 1H, Ph-C=CH–O), 7.92 (s, 1H, Ar–H), 7.84 (d, J = 7.8 Hz, 2H, Ar–H), 7.78 (d, J = 7.2 Hz, 2H, Ar–H), 7.55 (d, J = 7.2 Hz, 4H, Ar–H), 7.44 (d, J = 7.1 Hz, 1H, Ar–H), 3.46 (s, 2H, CH_2-CONH), 2.31 (s, 3H, C=C–CH_3), 1.21 (s, 3H, Ph-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.82 (s), 160.56 (s), 154.99 (s), 149.95 (s), 147.54 (s), 144.00 (s), 138.35 (s), 137.60 (s), 130.80 (s), 129.40 (s), 129.17 (s), 127.72 (s), 127.09 (s), 121.77 (s), 121.47 (s), 117.30 (s), 116.62 (s), 113.47 (s), 108.46 (s), 101.11 (s), 31.79 (s), 15.68 (s), 8.24 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{22}IN_2O_6S$ ($[M+H]^+$) 629.0238, found 629.0234.

Data for 3,4-difluoro-*N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-11**): White solid; Yield, 75%; m.p. 266–267 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.37 (d, J = 2.8 Hz, 1H, CO–NH–NH–SO_2), 10.17 (d, J = 3.0 Hz, 1H, CO–NH–NH–SO_2), 8.47 (s, 1H, Ph-C=CH–O), 8.16 (s, 1H, Ar–H), 7.83–7.78 (m, 4H, Ar–H), 7.68 (d, J = 8.8 Hz, 1H, Ar–H), 7.63–7.52 (m, 3H, Ar–H), 7.43 (t, J = 7.4 Hz, 1H, Ar–H), 3.49 (s, 2H, CH_2-CONH), 2.41 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.50 (s), 161.06 (s), 156.53 (s), 150.40 (s), 144.87 (s), 131.14 (s), 129.70 (s), 128.33 (s), 127.71 (s), 123.32 (s), 121.77 (s), 118.18 (s), 117.28 (s), 99.99 (s), 32.46 (s), 16.07 (s). HRMS (ESI) m/z: calcd. for $C_{26}H_{18}NaF_2N_2O_6S$ ($[M+Na]^+$) 547.0746, found 547.0745.

Data for N'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)naphthalene-2-sulfonohydrazide (**I-12**): White solid; Yield, 87%; m.p. 265–266 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.32 (d, J = 2.4 Hz, 1H, CO–NH–NH–SO_2), 10.03 (d, J = 2.6 Hz, 1H, CO–NH–NH–SO_2), 8.46 (s, 1H, Ph-C=CH–O), 8.43 (s, 1H, Ar–H), 8.10 (t, J = 8.5 Hz, 1H, Ar–H), 8.00 (d, J = 5.6 Hz, 2H, Ar–H), 7.94 (d, J = 7.9 Hz, 1H, Ar–H), 7.81 (dd, J = 15.0, 8.1 Hz, 3H, Ar–H), 7.74 (s, 1H, Ar–H), 7.62–7.53 (m, 4H, Ar–H), 7.45 (t, J = 7.2 Hz, 1H, Ar–H), 3.45 (s, 2H, CH_2-CONH), 2.21 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.75 (s), 160.55 (s), 155.97 (s), 149.83 (s), 149.65 (s), 144.32 (s), 136.11 (s), 134.38 (s), 131.50 (s), 130.63 (s), 129.20 (s), 128.68 (s), 127.84 (s), 127.64 (s), 127.19 (s), 123.23 (s), 122.76 (s), 121.22 (s), 117.70 (s), 116.70 (s), 116.39 (s), 99.46 (s), 31.87 (s), 15.43 (s). HRMS (ESI) m/z: calcd. for $C_{30}H_{23}N_2O_6S$ ($[M+H]^+$) 539.1271, found 539.1268.

Data for 1,1,1-trifluoro-*N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)methanesulfonohydrazide (**I-13**): Yellow solid; Yield, 84%; m.p. 139–140 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.69 (s, 1H, CO–NH–NH–SO_2), 8.48 (s, 1H, CO–NH–NH–SO_2), 8.21 (s, 1H, Ph-C=CH–O), 7.86–7.79 (m, 4H, Ar–H), 7.55 (t, J = 7.5 Hz, 2H, Ar–H), 7.43 (t, J = 7.4 Hz, 1H, Ar–H), 3.65 (s, 2H, CH_2-CONH), 2.51 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.21 (s), 160.69 (s), 156.11 (s), 150.25 (s), 150.04 (s), 144.39 (s), 130.70 (s), 130.64 (s), 129.20 (s), 127.82 (s), 127.24 (s), 122.99 (s), 121.30 (s), 117.60 (s), 116.87 (s), 116.74 (s), 99.57 (s), 32.14 (s), 15.68 (s). HRMS (ESI) m/z: calcd. for $C_{21}H_{15}NaF_3N_2O_6S$ ($[M+Na]^+$) 503.0495, found 503.0491.

Data for *N*'-(2-(3-(4-fluorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-14**): White solid; Yield, 92%; m.p. 234–235 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.28 (d, J = 3.0 Hz, 1H, CO–NH–NH–SO_2), 9.90 (d, J = 3.2 Hz, 1H, CO–NH–NH–SO_2), 8.46 (s, 1H, Ar–C=CH–O), 8.12 (s, 1H, Ar–H), 7.86 (dd, J = 8.7, 5.5 Hz, 2H, Ar–H), 7.80 (dd, J = 8.1, 6.6 Hz, 3H, Ar–H), 7.58 (t, J = 7.4 Hz, 1H, Ar–H), 7.49 (t, J = 7.5 Hz, 2H, Ar–H), 7.38 (t, J = 8.9 Hz, 2H, Ar–H), 3.47 (s, 2H, CH_2-CONH), 2.36 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.67 (s), 160.57 (s), 155.94 (s), 149.92 (s), 149.87 (s), 144.33 (s), 138.89 (s), 132.84 (s), 129.34 (s), 129.26 (s), 128.71 (s), 127.59 (s), 122.72 (s), 120.34 (s), 117.75 (s), 116.84 (s), 116.52 (s), 116.19 (s), 115.98 (s), 99.50 (s), 31.84 (s), 15.64 (s). HRMS (ESI) m/z: calcd. for $C_{26}H_{20}FN_2O_6S$ ($[M+H]^+$) 507.1021, found 507.1020.

Data for *N*'-(2-(5,9-dimethyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)methanesulfonohydrazide (**I-15**): Light yellow solid; Yield, 78%; m.p. 255–256 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.38 (s, 1H, CO–NH–NH–SO_2), 9.50 (s, 1H, CO–NH–NH–SO_2), 8.40 (s, 1H, Ph-C=CH–O), 7.91 (s, 1H, Ar–H), 7.75 (d, J = 6.9 Hz, 2H, Ar–H), 7.51 (d, J = 7.2 Hz, 2H, Ar–H), 7.42 (d, J = 7.0 Hz, 1H, Ar–H), 3.60 (s, 2H, CH_2-CONH), 2.92 (s, 3H, SO_2-CH_3), 2.45 (s, 3H, C=C–CH_3), 2.44 (s, 3H, Ph-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.93 (s), 160.69 (s), 154.93 (s), 150.03 (s), 147.50 (s), 143.95 (s), 130.76 (s), 129.13 (s), 127.69 (s), 127.04 (s), 121.68 (s), 121.40 (s), 117.60 (s), 116.61 (s), 113.58 (s), 108.40 (s), 39.88 (s), 32.20 (s), 15.70 (s), 8.13 (s). HRMS (ESI) m/z: calcd. for $C_{22}H_{21}N_2O_6S$ ($[M+H]^+$) 441.1115, found 441.1112.

Data for 4-iodo-*N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-16**): White solid; Yield, 62%; m.p. 261–262 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.29 (d, J = 2.9 Hz, 1H, CO–NH–NH–SO_2), 9.99 (d, J = 3.0 Hz, 1H, CO–NH–NH–SO_2), 8.47 (s, 1H, Ph-C=CH–O), 8.16 (s, 1H, Ar–H), 7.87–7.79 (m, 5H, Ar–H), 7.55 (dd, J = 12.0, 5.2 Hz, 4H, Ar–H), 7.44 (t, J = 7.4 Hz, 1H, Ar–H), 3.47 (s, 2H, CH_2-CONH), 2.37 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.31 (s), 161.09 (s), 156.56 (s), 150.43 (s), 150.30 (s), 144.85 (s), 139.00 (s), 138.11 (s),

131.16 (s), 129.86 (s), 129.72 (s), 128.33 (s), 127.73 (s), 123.40 (s), 121.79 (s), 118.25 (s), 117.33 (s), 117.04 (s), 101.73 (s), 100.05 (s), 32.38 (s), 16.14 (s). HRMS (ESI) m/z: calcd. for $C_{26}H_{20}IN_2O_6S$ ($[M+H]^+$) 615.0081, found 615.0080.

Data for 2,4-dichloro-*N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-17**): White solid; Yield, 75%; m.p. 225–226 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.31 (d, J = 2.3 Hz, 1H, CO–NH–NH–SO_2), 10.20 (d, J = 2.3 Hz, 1H, CO–NH–NH–SO_2), 8.47 (s, 1H, Ph-C=CH–O), 8.15 (s, 1H, Ar–H), 7.94 (d, J = 8.5 Hz, 1H, Ar–H), 7.80 (dt, J = 8.3, 2.0 Hz, 4H, Ar–H), 7.55 (dd, J = 10.5, 4.7 Hz, 2H, Ar–H), 7.51–7.41 (m, 2H, Ar–H), 3.45 (s, 2H, CH_2-CONH), 2.35 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.26 (s), 160.53 (s), 156.05 (s), 149.90 (s), 149.84 (s), 144.36 (s), 138.19 (s), 135.73 (s), 133.40 (s), 132.73 (s), 131.04 (s), 130.64 (s), 129.21 (s), 127.84 (s), 127.21 (s), 127.15 (s), 122.83 (s), 121.26 (s), 117.64 (s), 116.78 (s), 116.55 (s), 99.53 (s), 31.75 (s), 15.59 (s). HRMS (ESI) m/z: calcd. for $C_{26}H_{19}Cl_2N_2O_6S$ ($[M+H]^+$) 557.0335, found 557.0332.

Data for *N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)pyridine-3-sulfonohydrazide (**I-18**): White solid; Yield, 52%; m.p. 138–139 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.40 (s, 1H, CO–NH–NH–SO_2), 8.92 (d, J = 1.8 Hz, 1H, CO–NH–NH–SO_2), 8.73 (dd, J = 4.8, 1.5 Hz, 1H, Ph-C=CH–O), 8.47 (s, 1H, Ar–H), 8.17 (dt, J = 8.0, 3.2 Hz, 2H, Ar–H), 7.85–7.80 (m, 3H, Ar–H), 7.78 (s, 1H, Ar–H), 7.53 (dd, J = 7.5, 5.4 Hz, 3H, Ar–H), 7.44 (dd, J = 10.5, 4.3 Hz, 1H, Ar–H), 3.48 (s, 2H, CH_2-CONH), 2.38 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.49 (s), 161.07 (s), 156.53 (s), 153.72 (s), 150.42 (s), 150.40 (s), 148.36 (s), 144.85 (s), 136.06 (s), 131.14 (s), 129.71 (s), 128.33 (s), 127.73 (s), 124.30 (s), 123.34 (s), 121.78 (s), 118.11 (s), 117.31 (s), 117.12 (s), 117.08 (s), 100.02 (s), 32.41 (s), 16.12 (s). HRMS (ESI) m/z: calcd. for $C_{25}H_{20}N_3O_6S$ ($[M+H]^+$) 490.1067, found 490.1066.

Data for *N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)-2-(trifluoromethoxy)benzenesulfonohydrazide (**I-19**): White solid; Yield, 71%; m.p. 244–245 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.33 (d, J = 2.5 Hz, 1H, CO–NH–NH–SO_2), 10.11 (d, J = 2.5 Hz, 1H, CO–NH–NH–SO_2), 8.48 (s, 1H, Ph-C=CH–O), 8.16 (s, 1H, Ar–H), 7.94 (dd, J = 7.8, 1.6 Hz, 1H, Ar–H), 7.84–7.79 (m, 3H, Ar–H), 7.72–7.66 (m, 1H, Ar–H), 7.56 (t, J = 7.6 Hz, 2H, Ar–H), 7.45 (dd, J = 13.2, 7.6 Hz, 3H, Ar–H), 3.44 (s, 2H, CH_2-CONH), 2.34 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.06 (s), 160.79 (s), 156.04 (s), 149.91 (s), 149.85 (s), 144.38 (s), 135.14 (s), 131.78 (s), 131.14 (s), 130.64 (s), 129.22 (s), 127.84 (s), 127.24 (s), 126.84 (s), 122.82 (s), 121.28 (s), 121.05 (s), 117.60 (s), 116.83 (s), 116.57 (s), 99.53 (s), 31.65 (s), 15.54 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{20}F_3N_2O_7S$ ($[M+H]^+$) 573.0938, found 573.0935.

Data for 3-methyl-*N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-20**): White solid; Yield, 62%; m.p. 257–258 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (s, 1H, CO–NH–NH–SO_2), 9.86 (s, 1H, CO–NH–NH–SO_2), 8.48 (s, 1H, Ph-C=CH–O), 8.16 (s, 1H, Ar–H), 7.84–7.79 (m, 3H, Ar–H), 7.61 (s, 2H, Ar–H), 7.54 (d, J = 6.8 Hz, 2H, Ar–H), 7.43 (dd, J = 18.0, 10.9 Hz, 3H, Ar–H), 3.48 (s, 2H, CH_2-CONH), 2.39 (s, 3H, C=C–CH_3), 2.33 (s, 3H, Ph-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.66 (s), 160.58 (s), 156.02 (s), 149.92 (s), 149.83 (s), 144.36 (s), 138.93 (s), 138.32 (s), 133.47 (s), 130.64 (s), 129.21 (s), 128.59 (s), 127.83 (s), 127.79 (s), 127.23 (s), 124.73 (s), 122.82 (s), 121.27 (s), 117.78 (s), 116.84 (s), 116.60 (s), 99.51 (s), 31.91 (s), 20.70 (s), 15.60 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{23}N_2O_6S$ ($[M+H]^+$) 503.1271, found 503.1272.

Data for 4-methyl-*N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-21**): White solid; Yield, 61%; m.p. 256–257 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.24 (d, J = 3.4 Hz, 1H, CO–NH–NH–SO_2), 9.79 (d, J = 3.4 Hz, 1H, CO–NH–NH–SO_2), 8.47 (s, 1H, Ph-C=CH–O), 8.15 (s, 1H, Ar–H), 7.84–7.79 (m, 3H, Ar–H), 7.68 (d, J = 8.2 Hz, 2H, Ar–H), 7.55 (t, J = 7.6 Hz, 2H, Ar–H), 7.45 (d, J = 7.4 Hz, 1H, Ar–H), 7.27 (d, J = 8.1 Hz, 2H, Ar–H), 3.46 (s, 2H, CH_2–CO–NH), 2.36 (s, 3H, Ph-CH_3), 2.27 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.62 (s), 160.59 (s), 156.02 (s), 149.91 (s), 149.82(s), 144.36 (s), 143.08 (s), 135.86 (s), 130.64 (s), 129.21 (s), 129.14 (s), 127.83 (s), 127.73 (s), 127.21 (s), 122.81 (s), 121.26 (s), 117.78 (s), 116.85 (s), 116.56 (s), 99.50 (s), 31.84 (s), 20.91 (s), 15.60 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{23}N_2O_6S$ ($[M+H]^+$) 503.1271, found 503.1267.

Data for 4-cyano-*N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-22**): White solid; Yield, 74%; m.p. 253–254 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.42 (s, 1H, CO–NH–NH–SO_2), 8.42 (s, 1H, Ph-C=CH–O), 8.09 (s, 1H, CO–NH–NH–SO_2), 7.97 (s, 3H, Ar–H), 7.78 (d, J = 7.2 Hz, 3H, Ar–H), 7.72 (s, 1H, Ar–H), 7.53 (t, J = 7.4 Hz, 3H, Ar–H), 7.42 (t, J = 7.3 Hz, 1H, Ar–H), 3.47 (s, 2H, CH_2-CONH), 2.35 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.08 (s), 160.54 (s), 156.00 (s), 149.82 (s), 144.29 (s), 143.27 (s), 132.81 (s), 130.63 (s), 129.17 (s), 128.44 (s), 127.79 (s), 127.17 (s), 122.81 (s), 121.22 (s), 117.60 (s), 116.71 (s), 116.50 (s), 115.09 (s), 99.44 (s), 31.90 (s), 15.60 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{19}NaN_3O_6S$ ($[M+Na]^+$) 536.0887, found 536.0883.

Data for *N*'-(2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetyl)-4-(trifluoromethyl)benzenesulfonohydrazide (**I-23**): White solid; Yield, 85%; m.p.

259–260 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.39 (s, 1H, CO–NH–NH–SO_2), 10.23 (d, J = 2.4 Hz, 1H, CO–NH–NH-SO_2), 8.47 (s, 1H, Ph-C=CH–O), 8.13 (s, 1H, Ar–H), 8.01 (d, J = 8.2 Hz, 2H, Ar–H), 7.86 (d, J = 8.3 Hz, 2H, Ar–H), 7.82–7.77 (m, 3H, Ar–H), 7.55 (t, J = 7.6 Hz, 2H, Ar–H), 7.44 (t, J = 7.4 Hz, 1H, Ar–H), 3.47 (s, 2H, CH_2-CONH), 2.34 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.94 (s), 160.57 (s), 156.03 (s), 149.88 (s), 149.82 (s), 144.35 (s), 142.80 (s), 130.63 (s), 129.19 (s), 128.71 (s), 127.84 (s), 127.18 (s), 125.88 (s), 125.87 (s), 122.83 (s), 122.18 (s), 121.24 (s), 117.66 (s), 116.75 (s), 116.50 (s), 99.49 (s), 31.83 (s), 15.58 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{20}F_3N_2O_6S$ ($[M+H]^+$) 557.0989, found 557.0990.

Data for 4-(tert-butyl)-*N*'-(2-(3-(4-chlorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)acetyl)benzenesulfonohydrazide (**I-24**): White solid; Yield, 72%; m.p. 149–150 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 10.25 (d, J = 3.2 Hz, 1H, CO–NH–NH–SO_2), 9.76 (d, J = 3.3 Hz, 1H, CO–NH–NH–SO_2), 8.51 (s, 1H, Ar–C=CH–O), 8.10 (s, 1H, Ar–H), 7.83 (d, J = 8.4 Hz, 2H, Ar–H), 7.79 (s, 1H, Ar–H), 7.71 (d, J = 8.5 Hz, 2H, Ar–H), 7.59 (d, J = 8.4 Hz, 2H, Ar–H), 7.47 (d, J = 8.5 Hz, 2H, Ar–H), 3.47 (s, 2H, CH_2–CONH), 2.30 (s, 3H, C=C–CH_3), 1.16 (s, 9H, Ph-C(CH_3)$_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 167.60 (s), 160.76 (s), 155.98 (s), 155.83 (s), 149.96 (s), 149.78 (s), 144.89 (s), 135.72 (s), 132.37 (s), 129.55 (s), 129.16 (s), 128.95 (s), 127.64 (s), 125.50 (s), 122.53 (s), 120.16 (s), 117.92 (s), 116.89 (s), 116.42 (s), 99.56 (s), 34.66 (s), 30.77 (s), 30.60 (s), 15.66 (s). HRMS (ESI) m/z: calcd. for $C_{30}H_{28}ClN_2O_6S$ ($[M+H]^+$) 579.1351, found 579.1350.

General synthetic procedure for target compounds II

To a solution of compounds **9** (0.9 mmol) in anhydrous acetonitrile (20 mL) was added corresponding amine (0.9 mmol). Then, the mixture was stirred at room temperature for 6 h. After the reaction was completed (checked by TLC), the solvent was evaporated in vacuo, 15 mL of water was added and the mixture was extracted with ethyl acetate (3 × 10 mL). The organic layers were combined, dried with anhydrous sodium sulfate, and concentrated to give the crude product, which was further purified by chromatography on silica gel using petroleum ether/ethyl acetate (υ/υ, 6:1) as eluent to give the target compounds **II**.

Data for 2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)-*N*-(m-tolylcarbamothioyl)acetamide (**II-1**): Yellow solid; Yield, 73%; m.p. 190–191 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H, CO–NH–CS–NH), 11.76 (s, 1H, CO–NH–CS–NH), 8.46 (s, 1H, Ph-C=CH–O), 8.19 (s, 1H, Ar–H), 7.83–7.76 (m, 3H, Ar–H), 7.54 (t, J = 7.5 Hz, 2H, Ar–H), 7.44 (dd, J = 15.3, 8.2 Hz, 3H, Ar–H), 7.25 (t, J = 7.8 Hz, 1H, Ar–H), 7.04 (d, J = 7.3 Hz, 1H, Ar–H), 3.95 (s, 2H, CH_2-CONH), 2.57 (s, 3H, C=C–CH_3), 2.28 (s, 3H, Ph-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.50 (s), 172.23 (s), 160.73 (s), 156.08 (s), 150.48 (s), 149.91 (s), 144.38 (s), 138.08 (s), 137.65 (s), 130.62 (s), 129.19 (s), 128.45 (s), 127.83 (s), 127.21 (s), 126.90 (s), 124.46 (s), 122.94 (s), 121.28 (s), 121.10 (s), 117.39 (s), 116.83 (s), 116.67 (s), 99.59 (s), 34.94 (s), 20.86 (s), 15.79 (s). HRMS (ESI) m/z: calcd. for $C_{28}H_{23}N_2O_4S$ ($[M+H]^+$) 483.1373, found 483.1369.

Data for *N*-((2,4-dichlorophenyl)carbamothioyl)-2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetamide (**II-2**): Yellow solid; Yield, 81%; m.p. 227–228 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.29 (s, 1H, CO–NH–CS–NH), 12.02 (s, 1H, CO–NH–CS–NH), 8.45 (s, 1H, Ph-C=CH–O), 8.18 (s, 1H, Ar–H), 8.06 (d, J = 8.8 Hz, 1H, Ar–H), 7.83–7.77 (m, 3H, Ar–H), 7.70 (d, J = 2.2 Hz, 1H, Ar–H), 7.54 (t, J = 7.6 Hz, 2H, Ar–H), 7.48–7.41 (m, 2H, Ar–H), 3.97 (s, 2H, CH_2-CONH), 2.57 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.72 (s), 172.23 (s), 160.73 (s), 156.09 (s), 150.54 (s), 149.90 (s), 144.37 (s), 134.46 (s), 131.29 (s), 130.61 (s), 129.19 (s), 128.89 (s), 128.83 (s), 127.82 (s), 127.33 (s), 127.20 (s), 122.94 (s), 121.27 (s), 117.29 (s), 116.86 (s), 116.65 (s), 99.58 (s), 34.92 (s), 15.81 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{19}Cl_2N_2O_4S$ ($[M+H]^+$) 537.0437, found 537.0435.

Data for *N*-((4-fluorophenyl)carbamothioyl)-2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl) acetamide (**II-3**): Light yellow solid; Yield, 75%; m.p. 177–178 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H, CO–NH–CS–NH), 11.81 (s, 1H, CO–NH–CS–NH), 8.48 (s, 1H, Ph-C=CH–O), 8.21 (s, 1H, Ar–H), 7.82 (d, J = 6.7 Hz, 3H, Ar–H), 7.60 (dd, J = 8.2, 4.9 Hz, 2H, Ar–H), 7.55 (t, J = 7.6 Hz, 2H, Ar–H), 7.43 (t, J = 7.1 Hz, 1H, Ar–H), 7.21 (t, J = 8.7 Hz, 2H, Ar–H), 3.95 (s, 2H, CH_2-CONH), 2.58 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.24 (s), 172.07 (s), 160.75 (s), 156.10 (s), 150.52 (s), 149.93 (s), 144.42 (s), 130.62 (s), 129.21 (s), 127.85 (s), 127.23 (s), 126.84 (s), 122.97 (s), 121.30 (s), 117.39 (s), 116.88 (s), 116.69 (s), 115.43 (s), 115.21 (s), 99.63 (s), 34.93 (s), 15.81 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{20}FN_2O_4S$ ($[M+H]^+$) 487.1122, found 487.1119.

Data for *N*-((2,2-difluoroethyl)carbamothioyl)-2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetamide (**II-4**): White solid; Yield, 79%; m.p. 267–268 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.75 (s, 1H, CO–NH–CS–NH), 8.46 (s, 1H, Ph-C=CH–O), 8.42 (t, J = 5.7 Hz, 1H, Ar–H), 8.16 (s, 1H, Ar–H), 7.81 (d, J = 7.9 Hz, 2H, Ar–H), 7.77 (s, 1H, CO–NH–CS–NH), 7.54 (t, J = 7.4 Hz, 2H, Ar–H), 7.43 (t, J = 7.0 Hz, 1H, Ar–H), 6.01 (t, J = 56.0 Hz, 1H, CHF2), 3.61 (s, 2H, CH_2-CONH), 3.50 (t, J = 15.9 Hz, 2H, CH_2-CHF_2), 2.49 (s, 3H,

C=C–C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.69 (s), 160.81 (s), 155.99 (s), 149.95 (s), 149.67 (s), 144.29 (s), 130.66 (s), 129.19 (s), 127.81 (s), 127.19 (s), 122.79 (s), 121.25 (s), 118.50 (s), 116.94 (s), 116.55 (s), 114.48 (s), 99.47 (s), 41.08 (s), 33.84 (s), 15.64 (s). HRMS (ESI) m/z: calcd. for $C_{23}H_{19}F_2N_2O_4S$ ([M + H]$^+$) 457.1028, found 457.1027.

Data for *N*-((2,2-difluoroethyl)carbamothioyl)-2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl) acetamide (**II-5**): Light yellow solid; Yield, 84%; m.p. 235–236 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.22 (s, 1H, CO–NH–CS–N$\underline{H}$), 11.96 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.45 (s, 1H, Ar–C=C$\underline{H}$–O), 8.16 (s, 1H, Ar–$\underline{H}$), 7.92 (d, *J* = 7.9 Hz, 1H, Ar–$\underline{H}$), 7.85 (dd, *J* = 8.4, 5.5 Hz, 2H, Ar–$\underline{H}$), 7.78 (s, 1H, Ar–$\underline{H}$), 7.69 (d, *J* = 8.0 Hz, 1H, Ar–$\underline{H}$), 7.39 (dt, *J* = 17.6, 8.1 Hz, 3H, Ar–$\underline{H}$), 7.22 (t, *J* = 7.1 Hz, 1H, Ar–$\underline{H}$), 3.98 (s, 2H, C$\underline{H}_2$-CONH), 2.58 (s, 3H, C=C–C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.77 (s), 172.16 (s), 160.71 (s), 156.01 (s), 150.55 (s), 149.93 (s), 144.37 (s), 136.59 (s), 132.61 (s), 129.32 (s), 129.24 (s), 128.39 (s), 127.76 (s), 127.02 (s), 122.85 (s), 120.34 (s), 118.96 (s), 117.35 (s), 116.81 (s), 116.69 (s), 116.18 (s), 115.96 (s), 99.59 (s), 34.92 (s), 15.83 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{19}BrFN_2O_4S$ ([M + H]$^+$) 565.0227, found 565.0222.

Data for 2-(3-(4-chlorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)-*N*-((4-phenylbutyl)carbamothioyl)acetamide (**II-6**): Light yellow solid; Yield, 74%; m.p. 201–202 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.49 (s, 1H, Ar–C=C$\underline{H}$–O), 8.11 (s, 1H, Ar–$\underline{H}$), 7.96 (t, *J* = 5.4 Hz, 1H, Ar–$\underline{H}$), 7.83 (d, *J* = 8.4 Hz, 2H, Ar–$\underline{H}$), 7.75 (s, 1H, CO–NH–CS–N$\underline{H}$), 7.58 (d, *J* = 8.4 Hz, 2H, Ar–$\underline{H}$), 7.23 (t, *J* = 7.4 Hz, 2H, Ar–$\underline{H}$), 7.14 (dd, *J* = 17.7, 7.2 Hz, 3H, Ar–$\underline{H}$), 3.52 (s, 2H, C$\underline{H}_2$-CONH), 3.08 (dd, *J* = 12.4, 6.4 Hz, 2H, CSNH–C$\underline{H}_2$), 2.55 (t, *J* = 7.5 Hz, 2H, $CH_2CH_2CH_2C\underline{H}_2$-Ph), 2.46 (s, 3H, C=C–C$\underline{H}_3$), 1.55 (dt, *J* = 15.2, 7.7 Hz, 2H, $CH_2CH_2C\underline{H}_2$-CH_2Ph), 1.42 (dd, *J* = 14.3, 6.9 Hz, 2H, $CH_2C\underline{H}_2$-CH_2CH_2Ph). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.49 (s), 160.80 (s), 155.89 (s), 149.98 (s), 149.31 (s), 144.64 (s), 142.12 (s), 132.34 (s), 129.59 (s), 129.14 (s), 128.92 (s), 128.24 (s), 128.16 (s), 125.57 (s), 122.42 (s), 120.16 (s), 119.05 (s), 117.09 (s), 116.43 (s), 99.46 (s), 38.44 (s), 34.75 (s), 34.13 (s), 28.73 (s), 28.29 (s), 15.65 (s). HRMS (ESI) m/z: calcd. for $C_{31}H_{28}ClN_2O_4S$ ([M + H]$^+$) 559.1453, found 559.1449.

Data for 2-(3-(4-chlorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)-*N*-((3-methoxyphenyl)carbamothioyl)acetamide (**II-7**): Yellow solid; Yield, 87%; m.p. 210–211 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.37 (s, 1H, CO–NH–CS–N$\underline{H}$), 11.79 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.47 (s, 1H, Ar–C=C$\underline{H}$–O), 8.13 (s, 1H, Ar–$\underline{H}$), 7.81 (d, *J* = 8.3 Hz, 2H, Ar–$\underline{H}$), 7.75 (s, 1H, Ar–$\underline{H}$), 7.56 (d, *J* = 8.4 Hz, 2H, Ar–$\underline{H}$), 7.37 (s, 1H, Ar–$\underline{H}$), 7.27 (t, *J* = 8.1 Hz, 1H, Ar–$\underline{H}$), 7.15 (d, *J* = 7.9 Hz, 1H, Ar–$\underline{H}$), 6.80 (d, *J* = 6.5 Hz, 1H, Ar–$\underline{H}$), 3.94 (s, 2H, C$\underline{H}_2$-CONH), 3.72 (s, 3H, Ph-OC$\underline{H}_3$), 2.55 (s, 3H, C=C–C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.36 (s), 172.21 (s), 160.68 (s), 159.27 (s), 156.01 (s), 150.45 (s), 149.92 (s), 144.73 (s), 138.79 (s), 132.36 (s), 129.50 (s), 129.41 (s), 129.11 (s), 128.90 (s), 122.59 (s), 120.15 (s), 117.41 (s), 116.76 (s), 116.71 (s), 116.01 (s), 111.82 (s), 109.45 (s), 99.59 (s), 55.16 (s), 34.89 (s), 15.78 (s). HRMS (ESI) m/z: calcd. for $C_{28}H_{22}ClN_2O_5S$ ([M + H]$^+$) 533.0932, found 533.0931.

Data for *N*-((2,2-difluoroethyl)carbamothioyl)-2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)acetamide (**II-8**): White solid; Yield, 71%; m.p. 294–295 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.53 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.42 (s, 1H, Ar–C=C$\underline{H}$–O), 8.13–8.05 (m, 2H, Ar–$\underline{H}$), 7.84 (dd, *J* = 8.3, 5.6 Hz, 2H, Ar–$\underline{H}$), 7.73 (s, 1H, CO–NH–CS–N$\underline{H}$), 7.36 (t, *J* = 8.8 Hz, 2H, Ar–$\underline{H}$), 3.48 (s, 2H, C$\underline{H}_2$-CONH), 2.65–2.58 (m, 1H, C$\underline{H}$(CH_2)CH_2), 2.46 (s, 3H, C=C–C$\underline{H}_3$), 0.60 (d, *J* = 5.1 Hz, 2H, CH(C$\underline{H}_2$)CH_2), 0.41 (d, *J* = 2.2 Hz, 2H, CH(CH_2)C$\underline{H}_2$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 169.85 (s), 162.95 (s), 160.80 (s), 160.51 (s), 155.84 (s), 149.91 (s), 149.36 (s), 144.20 (s), 129.27 (s), 129.19 (s), 127.10 (s), 122.64 (s), 120.30 (s), 118.91 (s), 116.98 (s), 116.38 (s), 116.16 (s), 115.94 (s), 99.40 (s), 33.91 (s), 22.46 (s), 15.64 (s), 5.60 (s). HRMS (ESI) m/z: calcd. for $C_{24}H_{20}FN_2O_4S$ ([M + H]$^+$) 451.1122, found 451.1119.

Data for 2-(3-(4-fluorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)-*N*-((4-phenylthiazol-2-yl)carbamothioyl)acetamide (**II-9**): Light yellow solid; Yield, 67%; m.p. 257–258 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.86 (s, 1H, CO–NH–CS–N$\underline{H}$), 12.38 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.47 (s, 1H, Ar–C=C$\underline{H}$–O), 8.20 (s, 1H, Ar–$\underline{H}$), 7.86 (d, *J* = 6.8 Hz, 4H, Ar–$\underline{H}$), 7.82 (s, 1H, Ar–$\underline{H}$), 7.73 (s, 1H, S-C$\underline{H}$ = C), 7.41–7.34 (m, 4H, Ar–$\underline{H}$), 7.30 (t, *J* = 7.1 Hz, 1H, Ar–$\underline{H}$), 4.00 (s, 2H, C$\underline{H}_2$-CONH), 2.60 (s, 3H, C=C–C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.43 (s), 173.05 (s), 160.71 (s), 157.88 (s), 156.04 (s), 150.75 (s), 149.95 (s), 144.36 (s), 133.62 (s), 129.30 (s), 129.22 (s), 128.68 (s), 128.04 (s), 127.05 (s), 125.65 (s), 122.88 (s), 120.34 (s), 117.10 (s), 116.80 (s), 116.68 (s), 116.16 (s), 115.95 (s), 109.07 (s), 99.60 (s), 35.07 (s), 15.84 (s). HRMS (ESI) m/z: calcd. for $C_{30}H_{21}FN_3O_4S_2$ ([M + H]$^+$) 570.0952, found 570.0950.

Data for 2-(3-(4-fluorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)-*N*-((3-hydroxypropyl)carbamothioyl)acetamide (**II-10**): White solid; Yield, 88%; m.p. 242–243 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.42 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.43 (s, 1H, Ar–C=C$\underline{H}$–O), 8.10 (s, 1H, Ar–$\underline{H}$), 7.95 (t, *J* = 5.3 Hz, 1H, Ar–$\underline{H}$), 7.84 (dd, *J* = 8.2, 5.7 Hz, 2H, Ar–$\underline{H}$), 7.74 (s, 1H, CO–NH–CS–N$\underline{H}$), 7.36 (t, *J* = 8.8 Hz, 2H, Ar–$\underline{H}$), 4.42 (t, *J* = 5.1 Hz, 1H, O$\underline{H}$), 3.52 (s, 2H, C$\underline{H}_2$-CONH), 3.41 (dd, *J* = 11.6, 6.1 Hz, 2H, C$\underline{H}_2$-OH), 3.11 (dd, *J* = 12.6, 6.4 Hz, 2H, NH-C$\underline{H}_2$), 2.48 (s, 3H,

C=C–C$\underline{H}_3$), 1.60–1.51 (m, 2H, C$\underline{H}_2$-CH_2OH). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.66 (s), 160.82 (s), 155.85 (s), 149.94 (s), 149.37 (s), 144.21 (s), 129.27 (s), 129.19 (s), 127.08 (s), 122.63 (s), 120.30 (s), 118.93 (s), 117.02 (s), 116.39 (s), 116.16 (s), 115.95 (s), 99.41 (s), 58.38 (s), 35.99 (s), 34.11 (s), 32.36 (s), 15.64 (s). HRMS (ESI) m/z: calcd. for $C_{24}H_{22}FN_2O_5S$ ($[M+H]^+$) 469.1228, found 469.1223.

Data for 2-(3-(4-fluorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)-*N*-((4-morpholinophenyl)carbamothioyl)acetamide (**II-11**): Light yellow solid; Yield, 83%; m.p. 219–220 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.18 (s, 1H, CO–NH–CS–N$\underline{H}$), 11.69 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.45 (s, 1H, Ar–C=C$\underline{H}$–O), 8.15 (s, 1H, Ar–$\underline{H}$), 7.88–7.83 (m, 2H, Ar–$\underline{H}$), 7.78 (s, 1H, Ar–$\underline{H}$), 7.44 (d, J = 8.8 Hz, 2H, Ar–$\underline{H}$), 7.36 (t, J = 8.7 Hz, 2H, Ar–$\underline{H}$), 6.91 (d, J = 8.8 Hz, 2H, Ar–$\underline{H}$), 3.94 (s, 2H, C$\underline{H}_2$-CONH), 3.71 (s, 4H, N(CH_2)CH_2C$\underline{H}_2$(C$\underline{H}_2$)O), 3.08 (s, 4H, N(C$\underline{H}_2$)C$\underline{H}_2$$CH_2$($CH_2$)O), 2.56 (s, 3H, C=C–C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.12 (s), 172.07 (s), 160.71 (s), 155.98 (s), 150.43 (s), 149.91 (s), 149.19 (s), 144.33 (s), 129.22 (s), 127.01 (s), 124.90 (s), 122.82 (s), 120.32 (s), 116.72 (s), 116.16 (s), 115.95 (s), 114.65 (s), 99.55 (s), 66.00 (s), 48.22 (s), 34.90 (s), 15.78 (s). HRMS (ESI) m/z: calcd. for $C_{31}H_{27}FN_3O_5S$ ($[M+H]^+$) 572.1650, found 572.1644.

Data for *N*-((4-chlorophenethyl)carbamothioyl)-2-(5-methyl-7-oxo-3-(p-tolyl)-7H-furo[3,2-g]chromen-6-yl)acetamide (**II-12**): White solid; Yield, 85%; m.p. 194–195 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.48 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.38 (s, 1H, Ar–C=C$\underline{H}$–O), 8.08 (s, 1H, Ar–$\underline{H}$), 8.01 (t, J = 5.4 Hz, 1H, Ar–$\underline{H}$), 7.73 (s, 1H, CO–NH–CS–N$\underline{H}$), 7.67 (d, J = 7.9 Hz, 2H, Ar–$\underline{H}$), 7.33 (d, J = 7.8 Hz, 2H, Ar–$\underline{H}$), 7.29 (d, J = 8.3 Hz, 2H, Ar–$\underline{H}$), 7.21 (d, J = 8.3 Hz, 2H, Ar–$\underline{H}$), 3.49 (s, 2H, C$\underline{H}_2$-CONH), 3.27 (dd, J = 12.7, 6.5 Hz, 2H, NH-C$\underline{H}_2$), 2.70 (t, J = 7.0 Hz, 2H, NHC$\underline{H}_2$-C$\underline{H}_2$), 2.40 (s, 3H, C=C–C$\underline{H}_3$), 2.37 (s, 3H, Ph-C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.67 (s), 160.87 (s), 155.91 (s), 149.88 (s), 149.40 (s), 143.80 (s), 138.45 (s), 137.15 (s), 130.67 (s), 130.55 (s), 129.73 (s), 128.11 (s), 127.72 (s), 127.08 (s), 122.91 (s), 121.17 (s), 118.71 (s), 116.89 (s), 116.38 (s), 99.37 (s), 40.08 (s), 34.25 (s), 34.10 (s), 20.81 (s), 15.55 (s). HRMS (ESI) m/z: calcd. for $C_{30}H_{26}ClN_2O_4S$ ($[M+H]^+$) 545.1296, found 545.1292.

Data for *N*-((3-fluorophenyl)carbamothioyl)-2-(5-methyl-7-oxo-3-(p-tolyl)-7H-furo[3,2-g]chromen-6-yl) acetamide (**II-13**): Light yellow solid; Yield, 82%; m.p. 225–226 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H, CO–NH–CS–N$\underline{H}$), 11.88 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.39 (s, 1H, Ar–C=C$\underline{H}$–O), 8.14 (s, 1H, Ar–$\underline{H}$), 7.74 (d, J = 7.2 Hz, 2H, Ar–$\underline{H}$), 7.68 (d, J = 7.8 Hz, 2H, Ar–$\underline{H}$), 7.40 (dd, J = 16.3, 8.7 Hz, 2H, Ar–$\underline{H}$), 7.33 (d, J = 8.0 Hz, 2H, Ar–$\underline{H}$), 7.07 (t, J = 8.1 Hz, 1H, Ar–$\underline{H}$), 3.95 (s, 2H, C$\underline{H}_2$-CONH), 2.55 (s, 3H, C=C–C$\underline{H}_3$), 2.37 (s, 3H, Ph-C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 178.74 (s), 172.22 (s), 162.81 (s), 160.73 (s), 160.39 (s), 156.04 (s), 150.49 (s), 149.86 (s), 143.93 (s), 137.18 (s), 130.27 (s), 130.17 (s), 129.72 (s), 127.66 (s), 127.10 (s), 123.10 (s), 121.19 (s), 120.09 (s), 117.27 (s), 116.78 (s), 116.56 (s), 112.79 (s), 111.14 (s), 110.88 (s), 99.52 (s), 34.93 (s), 20.81 (s), 15.76 (s). HRMS (ESI) m/z: calcd. for $C_{28}H_{22}FN_2O_4S$ ($[M+H]^+$) 501.1279, found 501.1274.

Data for *N*-((2-chloropyridin-3-yl)carbamothioyl)-2-(3-(4-fluorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)acetamide (**II-14**): Light yellow solid; Yield, 72%; m.p. 297–298 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.34 (s, 1H, CO–NH–CS–N$\underline{H}$), 12.07 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.46 (d, J = 8.0 Hz, 1H, Ar–C=C$\underline{H}$–O), 8.43 (s, 1H, Ar–$\underline{H}$), 8.30 (d, J = 3.1 Hz, 1H, Ar–$\underline{H}$), 8.13 (s, 1H, Ar–$\underline{H}$), 7.84 (dd, J = 8.1, 5.7 Hz, 2H, Ar–$\underline{H}$), 7.75 (s, 1H, Ar–$\underline{H}$), 7.49 (dd, J = 7.9, 4.7 Hz, 1H, Ar–$\underline{H}$), 7.35 (t, J = 8.7 Hz, 2H, Ar–$\underline{H}$), 3.98 (s, 2H, C$\underline{H}_2$-CONH), 2.57 (s, 3H, C=C–C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.94 (s), 172.23 (s), 162.96 (s), 160.70 (s), 155.99 (s), 150.54 (s), 149.89 (s), 147.12 (s), 145.22 (s), 144.32 (s), 136.36 (s), 132.52 (s), 129.28 (s), 129.20 (s), 127.00 (s), 123.07 (s), 122.82 (s), 120.31 (s), 117.27 (s), 116.76 (s), 116.64 (s), 116.15 (s), 115.94 (s), 99.56 (s), 34.94 (s), 15.81 (s). HRMS (ESI) m/z: calcd. for $C_{26}H_{17}NaClFN_3O_4S$ ($[M+Na]^+$) 544.0505, found 544.0501.

Data for 2-(3-(4-fluorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)-*N*-((4-(p-tolyl)thiazol-2-yl)carbamothioyl)acetamide (**II-15**): Light yellow solid; Yield, 64%; m.p. 257–258 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.83 (s, 1H, CO–NH–CS–N$\underline{H}$), 12.35 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.43 (s, 1H, Ar–C=C$\underline{H}$–O), 8.16 (s, 1H, Ar–$\underline{H}$), 7.87–7.82 (m, 2H, Ar–$\underline{H}$), 7.78 (s, 1H, Ar–$\underline{H}$), 7.72 (d, J = 7.8 Hz, 2H, Ar–$\underline{H}$), 7.62 (s, 1H, S-C$\underline{H}$=C), 7.36 (t, J = 8.7 Hz, 2H, Ar–$\underline{H}$), 7.17 (d, J = 7.8 Hz, 2H, Ar–$\underline{H}$), 3.99 (s, 2H, C$\underline{H}_2$-CONH), 2.58 (s, 3H, C=C–C$\underline{H}_3$), 2.27 (s, 3H, Ph-C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 175.34 (s), 173.04 (s), 162.97 (s), 160.71 (s), 156.05 (s), 150.75 (s), 149.95 (s), 149.20 (s), 144.37 (s), 137.41 (s), 130.95 (s), 129.31 (s), 129.23 (s), 127.06 (s), 125.58 (s), 122.88 (s), 120.35 (s), 117.10 (s), 116.80 (s), 116.69 (s), 116.17 (s), 115.96 (s), 108.22 (s), 99.61 (s), 35.05 (s), 20.74 (s), 15.84 (s). HRMS (ESI) m/z: calcd. for $C_{31}H_{23}FN_3O_4S_2$ ($[M+H]^+$) 584.1109, found 584.1107.

Data for *N*-((3,5-dichlorophenyl)carbamothioyl)-2-(3-(4-fluorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)acetamide (**II-16**): White solid; Yield, 91%; m.p. 209–210 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.32 (s, 1H, CO–NH–CS–N$\underline{H}$), 11.95 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.44 (s, 1H, Ar–C=C$\underline{H}$–O), 8.14 (s, 1H, Ar–$\underline{H}$), 7.88–7.81 (m, 2H, Ar–$\underline{H}$), 7.76 (d, J = 4.5 Hz, 3H, Ar–$\underline{H}$), 7.44 (s, 1H, Ar–$\underline{H}$), 7.36 (t, J = 8.7 Hz, 2H, Ar–$\underline{H}$), 3.95 (s, 2H, C$\underline{H}_2$-CONH), 2.56 (s, 3H, C=C–C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.19 (s), 172.00 (s), 162.97 (s), 160.69 (s), 160.54 (s), 156.01 (s), 150.51 (s), 149.91 (s), 144.36 (s), 140.14

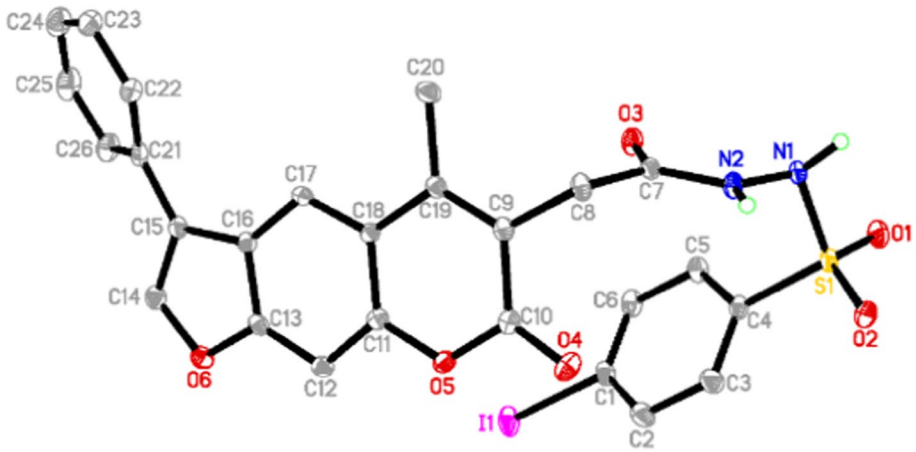


Fig. 5 X-ray crystal structure of compound **I-16** (CCDC: 2119934). The solvent molecule was omitted for clarity

(s), 133.58 (s), 129.30 (s), 129.22 (s), 127.05 (s), 125.63 (s), 123.06 (s), 122.85 (s), 120.33 (s), 117.28 (s), 116.74 (s), 116.64 (s), 116.16 (s), 115.95 (s), 99.59 (s), 34.93 (s), 15.80 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{18}Cl_2FN_2O_4S$ ($[M+H]^+$) 555.0343, found 555.0339.

Data for 2-(5,9-dimethyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl)-*N*-((3-nitrophenyl)carbamothioyl) acetamide (**II-17**): Light yellow solid; Yield, 77%; m.p. 140–141 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.42 (s, 1H, CO–NH–CS–NH), 11.91 (s, 1H, CO–NH–CS–NH), 8.67 (s, 1H, Ar–H), 8.35 (s, 1H, Ph-C=CH–O), 7.98 (d, J = 8.1 Hz, 1H, Ar–H), 7.90–7.83 (m, 2H, Ar–H), 7.70 (d, J = 7.5 Hz, 2H, Ar–H), 7.56 (t, J = 8.2 Hz, 1H, Ar–H), 7.46 (t, J = 7.6 Hz, 2H, Ar–H), 7.35 (t, J = 7.3 Hz, 1H, Ar–H), 3.89 (s, 2H, CH_2-CONH), 2.43 (s, 3H, C=C–CH_3), 2.41 (s, 3H, Ph-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.17 (s), 172.09 (s), 160.69 (s), 155.02 (s), 150.67 (s), 147.54 (s), 147.34 (s), 144.04 (s), 138.90 (s), 130.79 (s), 129.85 (s), 129.13 (s), 127.72 (s), 127.09 (s), 121.84 (s), 121.46 (s), 120.72 (s), 118.66 (s), 116.85 (s), 116.44 (s), 113.77 (s), 108.54 (s), 34.94 (s), 15.80 (s), 8.16 (s). HRMS (ESI) m/z: calcd. for $C_{28}H_{22}N_3O_6S$ ($[M+H]^+$) 528.1224, found 528,1219.

Data for 2-(3-(4-chlorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)-*N*-((2,4-dimethylphenyl)carbamothioyl)acetamide (**II-18**): Yellow solid; Yield, 95%; m.p. 234–235 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.89 (s, 1H, CO–NH–CS–NH), 11.77 (s, 1H, CO–NH–CS–NH), 8.48 (s, 1H, Ar–C=CH–O), 8.13 (s, 1H, Ar–H), 7.81 (d, J = 8.3 Hz, 2H, Ar–H), 7.75 (s, 1H, Ar–H), 7.56 (d, J = 8.3 Hz, 2H, Ar–H), 7.42 (d, J = 8.0 Hz, 1H, Ar–H), 7.05 (s, 1H, Ar–H), 7.00 (d, J = 8.1 Hz, 1H, Ar–H), 3.95 (s, 2H, CH_2-CONH), 2.56 (s, 3H, C=C–CH_3), 2.25 (s, 3H, Ph-CH_3), 2.12 (s, 3H, Ph-CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 179.56 (s), 172.04 (s), 160.68 (s), 156.01 (s), 150.40 (s), 149.92 (s), 144.73 (s), 136.19 (s), 134.14 (s), 132.84 (s), 132.36 (s), 130.86 (s), 129.51 (s), 129.12 (s), 128.90 (s), 126.59 (s), 126.21 (s), 122.58 (s), 120.15 (s), 117.50 (s), 116.77 (s), 116.72 (s), 99.58 (s), 34.88 (s), 20.52 (s), 17.47 (s), 15.80 (s). HRMS (ESI) m/z: calcd. for $C_{29}H_{24}ClN_2O_4S$ ($[M+H]^+$) 531,1140, found 531.1135.

Data for *N*-((2-chlorophenethyl)carbamothioyl)-2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl) acetamide (**II-19**): Light yellow solid; Yield, 73%; m.p. 202–203 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.42 (s, 1H, Ph-C=CH–O), 8.09 (d, J = 9.5 Hz, 2H, Ar–H), 7.79 (d, J = 7.5 Hz, 2H, Ar–H), 7.72 (s, 1H, CO–NH–CS–NH), 7.53 (t, J = 7.5 Hz, 2H, Ar–H), 7.44–7.37 (m, 2H, Ar–H), 7.30 (d, J = 6.8 Hz, 1H, Ar–H), 7.27–7.20 (m, 2H, Ar–H), 3.50 (s, 2H, CH_2-CONH), 3.30 (dd, J = 13.0, 6.6 Hz, 2H, CSNH–CH_2), 2.84 (t, J = 7.1 Hz, 2H, CSNH–CH_2CH_2), 2.43 (s, 3H, C=C–CH_3). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.69 (s), 160.83 (s), 155.92 (s), 149.90 (s), 149.41 (s), 144.21 (s), 136.71 (s), 133.06 (s), 131.12 (s), 130.67 (s), 129.18 (s), 128.10 (s), 127.78 (s), 127.16 (s), 122.71 (s), 121.22 (s), 118.72 (s), 116.95 (s), 116.40 (s), 99.38 (s), 38.58 (s), 34.09 (s), 32.82 (s), 15.62 (s). HRMS (ESI) m/z: calcd. for $C_{29}H_{24}ClN_2O_4S$ ($[M+H]^+$) 531.1140, found 531.1136.

Data for *N*-((2-hydroxyethyl)carbamothioyl)-2-(5-methyl-7-oxo-3-phenyl-7H-furo[3,2-g]chromen-6-yl) acetamide (**II-20**): Light yellow solid; Yield, 93%; m.p. 230–231 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.13 (s, 1H, CO–NH–CS–NH), 8.45 (s, 1H, Ph-C=CH–O), 8.14 (s, 1H, Ar–H), 7.99 (t, J = 5.3 Hz, 1H, Ar–H), 7.80 (d, J = 7.4 Hz, 2H, Ar–H), 7.75 (s, 1H, CO–NH–CS–NH), 7.54 (t, J = 7.6 Hz, 2H, Ar–H), 7.43 (t, J = 7.3 Hz, 1H, Ar–H), 4.69 (s, 1H, OH), 3.54 (s, 2H, CH_2-CONH), 3.13 (dd, J = 11.7,

5.8 Hz, 2H, CSNH–C$\underline{H}_2$), 2.92 (dd, J = 55.4, 50.2 Hz, 2H, C$\underline{H}_2$-OH), 2.48 (s, 3H, C=C–C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 168.84 (s), 160.87 (s), 155.93 (s), 149.92 (s), 149.41 (s), 144.25 (s), 130.67 (s), 129.20 (s), 127.81 (s), 127.19 (s), 122.74 (s), 121.24 (s), 118.91 (s), 117.00 (s), 116.47 (s), 99.42 (s), 59.79 (s), 41.68 (s), 34.03 (s), 15.65 (s). HRMS (ESI) m/z: calcd. for $C_{23}H_{21}N_2O_5S$ ($[M+H]^+$) 437.1166, found 437.1162.

Data for 2-(3-(4-chlorophenyl)-5-methyl-7-oxo-7H-furo[3,2-g]chromen-6-yl)-*N*-((pyridin-3-ylmethyl)carbamothioyl)acetamide (**II-21**): Yellow solid; Yield, 75%; m.p. 228–229 ℃. ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.60 (s, 1H, CO–N$\underline{H}$–CS–NH), 8.63 (dd, J = 14.0, 7.9 Hz, 3H, Ar–$\underline{H}$), 8.43 (s, 1H, Ar–C=C$\underline{H}$–O), 8.06 (s, 1H, Ar–$\underline{H}$), 7.93 (d, J = 7.6 Hz, 1H, Ar–$\underline{H}$), 7.78 (d, J = 8.2 Hz, 2H, Ar–$\underline{H}$), 7.68 (s, 1H, CO–NH–CS–N$\underline{H}$), 7.58 (d, J = 6.4 Hz, 1H, Ar–$\underline{H}$), 7.54 (d, J = 8.2 Hz, 2H, Ar–$\underline{H}$), 4.38 (d, J = 5.5 Hz, 2H, CSNH–C$\underline{H}_2$), 3.62 (s, 2H, C$\underline{H}_2$-CONH), 2.48 (s, 3H, C=C–C$\underline{H}_3$). ^{13}C NMR (101 MHz, DMSO-d_6) δ 171.85 (s), 169.36 (s), 160.82 (s), 155.86 (s), 149.89 (s), 149.57 (s), 145.77 (s), 145.46 (s), 144.58 (s), 138.08 (s), 132.30 (s), 129.50 (s), 129.09 (s), 128.82 (s), 124.58 (s), 122.39 (s), 120.08 (s), 118.68 (s), 116.95 (s), 116.44 (s), 99.41 (s), 39.87 (s), 34.21 (s), 15.67 (s). HRMS (ESI) m/z: calcd. for $C_{27}H_{21}ClN_3O_4S$ ($[M+H]^+$) 518.0936, found 518.0932.

X-ray diffraction

In order to confirm the structure of the title compounds, the crystal of compound **I-16** was cultured from the dimethyl sulfoxide-d_6, and the structure is shown in Fig. 5. All measurements were made on a Rigaku 007 Saturn 70 diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). Compound **I-16**: Triclinic, space group P-1, a = 10.3831(4) Å, b = 11.0228(3) Å, c = 13.5409(7) Å, α = 71.549(4)°, β = 78.465(4)°, γ = 82.838(3)°, V = 1437.26(11) Å^3, Z = 2, T = 113.15 K, μ(Mo Kα) = 1.308 mm^{-1}, $Dcalc$ = 1.600 g/cm^3. A total of 21,580 reflections were measured, of which 9668 were unique (R_{int} = 0.0438, R_{sigma} = 0.0556) in the range of 3.904° < 2Θ < 65.856° (−15 ≤ h ≤ 15, −16 ≤ k ≤ 16, −20 ≤ l ≤ 19). The structure was solved by direct method with the SHELXTL-97 program. All of the non-hydrogen atoms were refined by using anisotropic thermal displacement parameters and gave the final R indices R_1 = 0.0455 ($I > 2\sigma(I)$), wR_2 = 0.1194 (all data). The X-ray crystal structure data of **I-16** were available at the Cambridge Crystallographic Data Centre (CCDC: 2119934). The details of the crystallographic data and structure refinement parameters (Table S4) were listed in the supporting information.

Antifungal activity test

The in vitro antifungal activity of the title compounds **I** and **II** against *Alternaria solani*, *B. cinerea*, *C. arachidicola*, *Gibberella zeae*, *P. piricola*, *Pellicularia sasakii*, *Sclerotinia sclerotiorum* was evaluated at a concentration of 50 μg/mL according to the reported method [34]. Compounds with an inhibition over 60% were further evaluated for their median effective concentration (EC_{50}) according to the reference [35] by using psoralen and YZK-C22 as positive controls.

Molecular docking

The three-dimensional structure model of pyruvate kinase of *B. cinerea* (BcPK) was constructed by using the homology modeling, and PK structure of template protein was from *Saccharomyces cerevisiae* (PDB code: 1A3W). The human source of PK from *Homo sapiens* (HsPK, PDB code: 6TTF) was used to study the selective toxicity of the title compounds. The selected compound's molecular structure was drawn by ChemBioDraw Ultra 12.0 and energetically minimized by using Tripos SYBYL-X 2.0 software with default values. The docking program was performed by AutoDock Vina, and the detail docking procedures were according to the reported literatures [36, 37]. The molecular docking results was shown by Pymol.

Supplementary information

The ^{1}H NMR, ^{13}C NMR, HRMS spectra of target compounds, single crystal X-ray data for compound **I-16**, docking results of virtual screening and the calculation results of selective toxicity are reported in SI.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11030-022-10402-y.

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Declarations

Conflict of interest The authors declare no competing financial interest. Dedicated to the 100th Anniversary of Chemistry at Nankai University. Dedicated to the 60th Anniversary of Institute of Elemento-Organic Chemistry (Nankai University). Dedicated to our distinguished professor Zhengming Li (January 2, 1931–October 4, 2021) for his achievements and contributions to pesticide science and pesticide industry.

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