Design, Synthesis, and Antifungal Evaluation of Novel Coumarin-Pyrrole Hybrids

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Abstract: A series of coumarin derivatives bearing a pyrrole scaffold were designed, prepared and assessed for their in *vitro* antifungal activities against six phytopathogenic fungi. The antifungal activity screening results suggest that some synthesized hybrids exhibited potential fungicidal activities against the tested fungi. In particular, compounds **6j**, **6k**, **6o**, **6p** and **6r** displayed significant antifungal effects against *Rhizoctorzia solani*, and possessed EC_{50} values of 3.94, 7.75, 6.38, 6.25 and 7.67 μg/ mL, respectively. The above activities are more potent than the commercialized fungicide Boscalid (11.52 μg/mL) and Osthole (9.79 μg/mL). These results provide a significant reference for further rational design of coumarin-based fungicides.

Introduction

China has a vast territory, a wide variety of crops, but crop diseases are a serious threat to agricultural production. After a series of metabolic changes in a plant, chemical metabolites become non-toxic and harmless substances, some still remain quite toxic, or metabolize new toxic substances, and even become carcinogenic teratogenic substances. The long-term overuse of traditional fungicides, has been brought about the fungal resistances and environment pollution [1].

Coumarin and its analogues are important secondary metabolites, which are broadly distributed in the roots, flowers and fruits. Many plants can synthesize coumarins, such as Calendula officinalis, Angelica dahurica and Zanthoxylum schinifolium. In addition, some fungi (such as Armillariella tabescens, Fomitopsis officinalis) and bacteria (such as Streptomyces niveus, Escherichia coil) can also synthesize coumarins [2]. Due to the unique chemical structure of coumarins, their skeletons can interact with many receptors in the organism noncovalent, they usually display a variety of biological activities, including anti-depression, anti-oxidation, anti-inflammatory, antibacterial, anti-tumor, anti-asthmatic, anti-viral and anti-coagulant effects, and are effective ingredients of many traditional Chinese medicines. Many coumarin-like natural products such as osthole, umbelliferone, pre-caprolactone, coralin, alizarin and sulphate have significant inhibitory effects on plant pathogenic fungi [3-14].

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Pyrrole is an important framework structure in pharmaceutical chemistry, which can react with many biomolecules through hydrogen bond and π-π stacking interaction. This basic structural fragment is widely found in drug molecules, natural products and several biological molecular structures [15], such as chlorophyll, hemoglobin, myoglobin, cytochrome and vitamin B12. Pyrrole substructures exhibit different biological activities, including anti-inflammatory, anti-bacterial, anti-fungal, anti-tumor, anti-depression, anti-viral, insecticidal and protease inhibitor [16-21]. For example, pyrrolactin A has obvious antibiotic activity [22]; diphthalamide B and its derivatives showed significant antibacterial activity [23-26]. Thus, hybridization of pyrrole and coumarin into one single molecule may provide a key basis for the development of promissing agrochemicals.

Our previous research results showed that various structural modifications to osthole could improve its inhibition activity against certain phytopathogenic fungi in *vitro* [27-32]. Especially, we found that some 7-pyrrole substituted coumarin derivatives displayed stronger antifungal activity against *Rhizoctorzia solani* than positive control Osthole [33]. Based on the aforementioned results and as a part of continuous program to optimize 6-pyrrole substituted coumarin hybrids as novel fungicides precursor compounds, a novel series of pyrrole-coumarin hybrids was designed (Fig.1), prepared and assessed for their in *vitro* fungicidal activity against six phytopathogenic fungi.

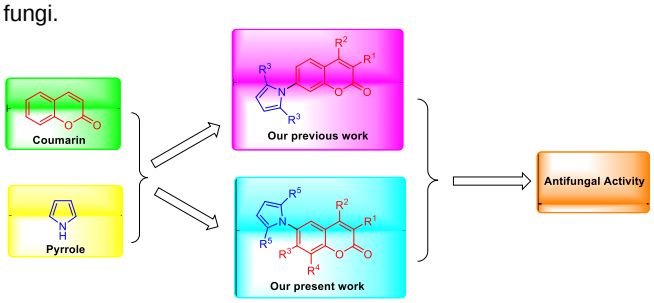


Figure 1. Illustration of the design strategy for pyrrole-coumarin hybrids.

Results and Discussion

Chemistry The general synthetic route for the target coumarin-pyrrole hybrids **6a**-**6y** was illustrated in scheme 1. Using substituted and unsubstituted ethyl acetoacetate **1** and phenol derivatives **2** as starting materials, a series of 2-aminocoumarin derivatives **5** were synthesized via three steps, including Pechmann condensation, nitration and reduction reaction. Subsequently, intermediate **5** was reacted with 2,5-dimethoxytetrahydrofuran in H_2O in the presence of $FeCl_3$ at 60 ^oC to form the desired hybrids (**6a**-**6m**, **6w**-**6y**). The hybrids **6n**-**6v** were achieved by treatment of intermediate **5** with acetonylacetone in HOAc at 60 ^oC. The structures of the synthesized compounds were elucidated by HRMS and NMR spectroscopy. In addition, compounds **6e** were further determined through X-ray diffraction crystallography (Fig. 2).

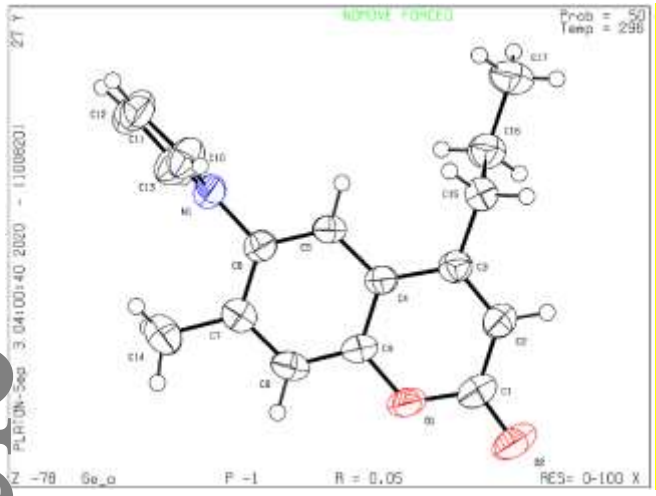


Figure 2. X-ray structures of compounds **6e**.

In vitro antifungal activity assessment. The six phytopathogenic fungi *Botrytis cinerea*, *Rhizoctorzia solani*, *Alternaria solani*, *Gibberella zeae*, *Alternaria leaf spot* and *Cucumber anthrax*, which are stored in the Laboratory of Plant Disease Control at Nanjing Agricultural University. The above phytopathogenic fungi are selected to evaluate the fungicidal effects of target compounds. Fungicidal effects of the coumarin-pyrrole hybrids **6a**-**6y** and the positive control (Boscalid and Osthole) were tested at 50 μg/mL based on the mycelium growth rate method, and the preliminary results were presented in Table 2(For intermediates **4** and **5**, see Table 1S in supplementary information). As shown in Table 2, most of the synthesized compounds displayed a certain degree of activity against all the tested fungi. Among them, compounds **6j**, **6k**, **6o**, **6p** and **6r** showed significant activity against *Rhizoctorzia solani* at 50.0 μg/mL, with the corresponding inhibition rates of 78%, 68%, 75%, 77% and 68%, which are better than or similar that of Osthole (68%). In addition, compound **6j** effectively inhibited the mycelium growth of *Botrytis cinerea* and *Cucumber anthrax*, with the inhibition rates of 59% and 53%, respectively, which are better than that of Osthole (47% and 17%, respectively).

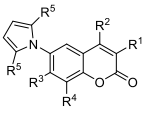
Aiming to learn more about the fungicidal activities of the synthesized compounds, we tested the corresponding EC_{50} values of compounds **6j**, **6k**, **6o**, **6p** and **6r** against *Rhizoctorzia solani*. As shown in Table 3, the EC_{50} values of the above compounds reached 3.94, 7.75, 6.38, 6.25 and 7.67 μg/mL, respectively, which are more potent than that of Boscalid (11.52 μg/mL) and Osthole (9.79 μg/mL).

Scheme 1. Synthesis of the coumarin-pyrrole hybrids. Reagents and conditions: (a) 70% H_2SO_4, 0 ^oC(**3a**-**3i**); 98% H_2SO_4, 0 ^oC (**3j**-**3m**); (b) H_2SO_4, KNO_3, -10 ^oC; (c) Fe, HOAc, EtOH, H_2O, rt (**5a**-**5i**); $SnCl_2$, HCl, EtOH, reflux (**5j**-**5m**); (d) 2,5-dimethoxytetrahydrofuran, $FeCl_3$, H_2O, 60^oC (**6a**-**6m, 6w-6y**); acetonylacetone, HOAc, 60^oC (**6n**-**6v**)

Structure-activity relationships. The antifungal results in Table 2 showed that most of the coumarin-pyrrole hybrids exhibited unsatisfied activities, but we still can summarize the structure-activity relationships. Firstly, most of the synthesized compounds exhibited better inhibition effects against *Botrytis cinerea* and *Rhizoctorzia solani* than that of other tested fungi. Secondly, the fungicidal activities of target compounds against the tested phytopathogenic fungi could generally decrease when introducing the alkyl or halogen group at the R^1 position and no substituents at the R^5 position. The presence of a methyl substituent at the R^5 position, the corresponding compounds **6s** and **6v** exhibited the similar regulation. Thirdly, the title compounds bearing a OH group at R^3 position, methyl group at R^4 position and H at R^5 position, such as **6j** and **6k**, displayed better inhibition effects against *Botrytis cinerea*, *Gibberella zeae* and *Rhizoctorzia solani* than those bearing a methyl group at R^3 position, a H at R^4 and R^5 position(**6b** and **6e**).

Crystal. The Single-crystal of **6e** was prepared by the emulsion solvent evaporation method from hexane: trichloromethane=3:1(v/v). The Single-crystal X-ray diffraction analysis of **6e** was performed with a Bruker D8 QUEST diffractometer with graphite-monochromated Mo-Ka radiation (λ=0.71073 Å) at 296(2)K. Data reduction and absorption corrections were carried out on the SAINT and SADABS software packages, respectively. The structures were determined by direct methods and refined by the full matrix least-squares based on F2 using SHELXL-2018 programme package. The non-hydrogen atoms were refined anisotropically. All hydrogen atoms were placed at the calculated positions and refined as riding on the parent atoms. The data collection, structure refinement and crystallography are summarized in the Supporting Information. The ellipsoid contour % probability levels in the caption for the image of the X-ray structure was 30% (Fig 2).

Table 1. Structures and yields of 6-pyrrolecoumarins.



Compound	R^1	R^2	R^3	R^4	R^5	Yield (%)
6a	H	H	H	H	H	76

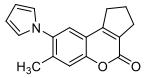
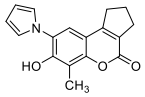
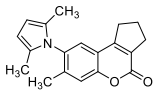
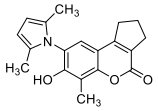
6b	H	CH_3	CH_3	H	H	71
6c	H	CF_3	CH_3	H	H	59
6d	H	CH_2Cl	CH_3	H	H	53
6e	H	$CH_3CH_2CH_2$	CH_3	H	H	87
6f	CH_3	CH_3	CH_3	H	H	59
6g	CH_3CH_2	CH_3	CH_3	H	H	85
6h						54
6i	Cl	CH_3	CH_3	H	H	41
6j	H	CH_3	OH	CH_3	H	43
6k	H	$CH_3CH_2CH_2$	OH	CH_3	H	44
6l	CH_3CH_2	CH_3	OH	CH_3	H	28
6m						56
6n	H	H	H	H	CH_3	67
6o	H	CH_3	CH_3	H	CH_3	59
6p	H	CF_3	CH_3	H	CH_3	78
6q	H	CH_2Cl	CH_3	H	CH_3	47
6r	H	$CH_3CH_2CH_2$	CH_3	H	CH_3	35
6s	CH_3	CH_3	CH_3	H	CH_3	43
6t	CH_3CH_2	CH_3	CH_3	H	CH_3	36
6u						22
6v	Cl	CH_3	CH_3	H	CH_3	35
6w	H	$CH_3CH_2CH_2$	OH	CH_3	CH_3	62
6x	CH_3CH_2	CH_3	OH	CH_3	CH_3	28
6y						74

Table 2. Antifungal activity of target compounds(inhibitory rate, %)[a]

Species[b]	BOT	ALT	GIB	RHI	ALS	CUC
Compound Dose(μg/mL)	50	50	50	50	50	50
6a	32	20	27	68	0	30
6b	25	8	20	42	4	38
6c	23	8	22	45	13	11
6d	10	17	5	44	7	9
6e	18	0	11	27	40	11
6f	18	7	8	35	15	2
6g	9	0	8	28	9	4
6h	7	0	8	10	13	15
6i	9	0	13	2	12	11
6j	59	16	52	78	1	53
6k	42	17	24	68	2	0
6l	27	0	20	50	3	9
6m	25	0	17	56	7	2
6n	38	0	27	42	22	51
6o	34	0	13	75	9	15
6p	50	16	42	77	39	19
6q	30	0	8	38	6	19
6r	32	3	5	68	6	15
6s	9	0	5	20	0	6
6t	43	3	27	72	30	23
6u	5	0	6	37	0	6
6v	25	0	5	42	0	17
6w	63	2	30	40	20	18
6x	48	0	36	69	11	16
6y	34	0	13	59	11	3
Boscalid[c]	100	38	18	92	93	23
Osthole[c]	47	3	45	68	15	17

[a] Average of three replicates. [b] BOT Botrytis cinerea, ALT Alternaria solani, GIB Gibberella zeae, RHI Rhizoctorzia solani, ALS Alternaria leaf spot, CUC Cucumber anthrax. [c] A commercial agricultural fungicides boscalid and osthole were used for comparison of antifungal activities.

Table 3. EC_{50} values of some target compounds against Rhizoctorzia solani[a].

Compound	Regression equation	R	EC_{50} (μg/mL)	95% confidence interval

6a	Y=2.1302+2.0718x	0.9997	24.2783	22.4976-26.2001
6j	Y=4.1113+1.4914x	0.9863	3.9437	3.2149-4.8376
6k	Y=4.2795+0.8101x	0.9949	7.7521	6.7126-8.9406
6o	Y=3.5803+1.7636x	0.9557	6.3825	3.9795-10.2366
6p	Y=4.2405+0.9547x	0.9766	6.2457	4.6584-8.3739
6r	Y=3.6410+1.5364x	0.9897	7.6655	6.0046-9.7859
6t	Y=3.7873+1.0041x	0.9993	16.1358	14.6206-17.8080
Boscalid[b]	Y=4.3785+0.5855x	0.9906	11.5212	9.4778-14.0052
Osthole[b]	Y=4.2160+0.7915x	0.9928	9.7850	8.2946-11.5433

[a] Average of three replicates. [b] A commercial agricultural fungicides boscalid and osthole were used for comparison of antifungal activities.

Conclusions

In summary, aiming to develop novel structure coumarin derivatives against plant fungi, we designed and synthesized a novel series of coumarin derivatives bearing a pyrrole moiety. The fungicidal activities of the target compounds against six phytopathogenic fungi in *vitro* were evaluated. All hybrids exhibited considerable activities against the tested fungi, among them, compounds **6j**, **6k**, **6o**, **6p** and **6r** showed remarkable fungicidal activities against Rhizoctorzia solani, and possessed the EC_{50} values of 3.94, 7.75, 6.38, 6.25, and 7.67 μg/ mL, respectively, which are more potent than Boscalid (11.52 μg/mL) and Osthole (9.79 μg/mL). The structure-activity relationship may provide useful reference for the further development of more efficient coumarin-based agricultural fungicides.

Experimental Section

Chemistry. Melting points of the target compounds were carried out on an uncorrected WRS-1B digital melting point apparatus (Jingmi Science, China). Using $CDCl_3$, Acetone-d_6 and DMSO-d_6 as a solvent and tetramethylsilane as an internal standard, a Bruker 400 spectrometer (Bruker, Germany) was used for characterizing the ^{1}H-NMR and ^{13}C-NMR spectra of title compounds. Mass spectra were characterized on a TRACE 2000 spectrometer (Finnigan, America). X-Rays were carried out at 296 K on a Bruker SMART APEX2 CCD area detector diffractometer. All reagents and solvents were analytically pure and were not pretreatment.

The general procedure for the preparation of intermediates 5a-5i.

The precursors **3** and **4** were prepared via literature methods [34-35]. A mixture of precursor **4** (10.0 mmol) and iron power (30.0 mmol, 3.0 equiv) in EtOH (20.0 mL), HOAc (20.0 mL), H_2O (10.0 mL) was reacted at room temperature, and the reaction was monitored by TLC. After the reaction finished, the precipitated solid was filtered, washed with ethyl acetate (50.0 mL), and the filtrate was extracted with ethyl acetate (3 × 50.0 mL). Using the saturated aqueous Na_2CO_3 to wash the combined extracts until it reached pH 8.0, dried over with Na_2SO_4 and filtrated, and the filtrate was concentrated in vacuo to form the target compounds in 46%-97% yields.

The general procedure for the preparation of intermediates 5j-5m.

A solution of precursor **4** (10.0 mmol) in EtOH (10.0 mL), HCl (10.0 mL) was added $SnCl_2$ (10.0 mmol), then refluxed for 0.5 h. The mixture was cooled to -20 °C for 24 h after the reaction finished, and the precipitated solid was filtered, washed with saturated aqueous Na_2CO_3 (150.0 mL), and the solid was dissolved into isopropanol (100.0 mL). The precipitated solid was filtered, and the filtrate was concentrated in vacuo to generate the title compounds in 71%-83% yields.

The general procedure for preparing target compounds 6a-6m, 6w-6y.

A mixture of precursor **5** (1.0 mmol) and 2,5-dimethoxytetrahydrofuran (1.2 mmol, 1.2 equiv), and fused $FeCl_3 \cdot 7H_2O$ (5.0 mol%) in H_2O (5.0 mL) was stirred at 60 °C for 24 h. After the reaction completed, the mixture was cooled to room temperature, filtered and extracted with dichloromethane (3 × 20.0 mL). The combined extracts were dried over with Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1 to 4:1, v/v) to obtain the title compounds in 28%-87% yields (Table 1).

6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6a)** [36]: white solid; mp: 144.3-145.6 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 9.6 Hz, 1H), 7.54 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.46 (d, *J* = 2.5 Hz, 1H), 7.36 (d, *J* = 8.9 Hz, 1H), 7.06 (t, *J* = 2.1 Hz, 2H), 6.47 (d, *J* = 9.6 Hz, 1H), 6.39 – 6.34 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 151.6, 142.9, 137.3, 124.2, 119.5, 118.8, 118.1, 117.8, 111.1; HRMS: (*m/z*) *Anal.* Calcd for $C_{13}H_{10}NO_2$ $[M + H]^+$, 212.0706; Found, 212.0706.

4,7-dimethyl-6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6b)**: white solid; mp: 145.5-146.9 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.20 (s, 1H), 6.78 (t, *J* = 2.1 Hz, 2H), 6.32 (t, *J* = 2.1 Hz, 2H), 6.24 (d, *J* = 1.0 Hz, 1H), 2.38 (d, *J* = 1.1 Hz, 3H), 2.25 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 152.2, 151.9, 139.1, 137.0, 122.5, 122.2, 118.7, 118.2, 114.9, 109.3, 18.5, 18.0; HRMS: (*m/z*) *Anal.* Calcd for $C_{15}H_{14}NO_2$ $[M + H]^+$, 240.1019; Found, 240.1019.

7-methyl-6-(1H-pyrrol-1-yl)-4-(trifluoromethyl)-2H-chromen-2-one **(6c)**: yellow solid; mp: 168.7-170.3 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.35 (s, 1H), 6.79 (t, *J* = 2.0 Hz, 3H), 6.36 (t, *J* = 2.1 Hz, 2H), 2.31 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.6, 153.1, 141.2, 141.1 (q, *J* = 33.2 Hz), 138.0, 123.0 (q, *J* = 2.2 Hz), 122.3, 121.4 (q, *J* = 276.4 Hz), 119.5, 116.0 (q, *J* = 5.7Hz), 111.8, 109.8, 18.4; HRMS: (*m/z*) *Anal.* Calcd for $C_{15}H_{11}F_3NO_2$ $[M + H]^+$, 294.0736; Found, 294.0746.

4-(chloromethyl)-7-methyl-6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6d)**: white solid; mp: 153.7-154.3 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.30 (s, 1H), 6.78 (t, *J* = 2.0 Hz, 2H), 6.57 (s, 1H), 6.36 (t, *J* = 2.0 Hz, 2H), 4.61 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.2, 152.8, 149.2, 140.0, 137.5, 122.4, 122.2, 119.4, 116.0, 115.7, 109.7, 41.2, 18.3; HRMS: (*m/z*) *Anal.* Calcd for $C_{15}H_{13}ClNO_2$ $[M + H]^+$, 274.0629; Found, 274.0628.

7-methyl-4-propyl-6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6e)**: white solid; mp: 130.3-130.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 6.78 (t, *J* = 2.1 Hz, 2H), 6.36 (t, *J* = 2.1 Hz, 2H), 6.29 (s, 1H), 2.74 – 2.66 (m, 2H), 2.25 (s, 3H), 1.78 – 1.67 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 155.5, 152.5, 139.0, 137.0, 122.3, 119.0, 117.6, 113.7, 109.3, 33.5, 21.2, 18.0, 13.9; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{18}NO_2$ $[M + H]^+$, 268.1332; Found, 268.1333.

3,4,7-trimethyl-6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6f)**: white solid; mp: 182.2-183.3 ℃; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.60 (s, 1H), 7.29 (s, 1H), 6.89 (t, *J* = 2.1 Hz, 2H), 6.26 (t, *J* = 2.1 Hz, 2H), 2.46 (s, 3H), 2.25 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 150.9, 145.5, 137.7, 137.0, 122.5, 122.4, 122.4, 119.0, 118.5, 109.3, 18.0, 15.2, 13.6; HRMS: (*m/z*) *Anal.* Calcd for $C_{16}H_{16}NO_2$ $[M + H]^+$, 254.1176; Found, 254.1177.

3-ethyl-4,7-dimethyl-6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6g)**: white solid; mp: 170.1-170.3 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.19 (s, 1H), 6.77 (t, *J* = 2.0 Hz, 2H), 6.34 (t, *J* = 2.0 Hz, 2H), 2.69 (q, *J* = 7.6 Hz, 2H), 2.37 (s, 3H), 2.24 (s, 3H), 1.15 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 151.0, 145.0, 137.7, 137.0, 128.2, 122.6, 122.3, 119.1, 118.4, 109.2, 21.1, 17.9, 14.6, 13.1; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{18}NO_2$ $[M + H]^+$, 268.1332; Found, 268.1335.

7-methyl-8-(1H-pyrrol-1-yl)-2,3-dihydrocyclopenta[c]chromen-4(1H)-one **(6h)**: white solid; mp: 208.7-209.2 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.27 (s, 1H), 6.77 (t, *J* = 2.1 Hz, 2H), 6.34 (t, *J* = 2.1 Hz, 2H), 1.78 – 1.67 (m, 2H), 2.93 (t, *J* = 7.5 Hz, 2H), 2.26 (s, 3H), 2.24 – 2.19 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 155.6, 153.1, 138.1, 137.0, 128.2, 122.7, 122.4, 118.6, 117.2, 109.4, 32.1, 30.8, 22.6, 18.3; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{16}NO_2$ $[M + H]^+$, 266.1176; Found, 266.1174.

3-chloro-4,7-dimethyl-6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6i)**: white solid; mp: 221.7-222.4 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.26 (s, 1H), 6.78 (t, *J* = 2.0 Hz, 1H), 6.35 (t, *J* = 2.0 Hz, 2H), 2.54 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 150.2, 147.3, 139.4, 137.8, 122.9, 122.3, 121.0, 118.9, 118.2, 109.6, 18.2, 16.3; HRMS: (*m/z*) *Anal.* Calcd for $C_{15}H_{13}ClNO_2$ $[M + H]^+$, 274.0629; Found, 274.0635.

7-hydroxy-4,8-dimethyl-6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6j)**: white solid; mp: 196.9-197.7 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.85 (t, *J* = 2.1 Hz, 2H), 6.44 (t, *J* = 2.1 Hz, 2H), 5.98 (s, 1H), 2.52 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.3, 152.1, 150.2, 147.8, 125.6, 122.2, 120.1, 118.8, 114.0, 113.1, 111.4, 16.4, 8.9; HRMS: (*m/z*) *Anal.* Calcd for $C_{15}H_{14}NO_3$ $[M + H]^+$, 256.0968; Found, 256.0949.

7-hydroxy-8-methyl-4-propyl-6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6k)**: white solid; mp: 213.2-213.8 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (s, 1H), 6.85 (t, *J* = 2.0 Hz, 2H), 6.43 (t, *J* = 2.0 Hz, 2H), 6.17 (s, 1H), 5.98 (s, 1H), 2.66 (t, *J* = 7.5 Hz, 2H), 2.38 (s, 3H), 1.76 – 1.65 (m, 2H), 1.03 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 156.2, 152.5, 152.0, 125.0, 122.2, 119.4, 114.0, 112.6, 111.7, 111.1, 33.9, 21.5, 14.0, 8.8; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{18}NO_3$ $[M + H]^+$, 284.1281; Found, 284.1279.

3-ethyl-7-hydroxy-4,8-dimethyl-6-(1H-pyrrol-1-yl)-2H-chromen-2-one **(6l)**: white solid; mp: 189.2-190.2 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 6.84 (t, *J* = 2.1 Hz, 2H), 6.40 (t, *J* = 2.1 Hz, 2H), 6.12 (s, 1H), 2.66 (q, *J* = 7.5 Hz, 2H), 2.36 (s, 3H), 2.34 (s, 3H), 1.13 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, 151.2, 150.7, 145.6, 125.8, 124.9, 122.3, 119.7, 114.0, 113.4, 110.8, 20.9, 14.7, 13.2, 8.7; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{18}NO_3$ $[M + H]^+$, 284.1281; Found, 284.1281.

7-hydroxy-6-methyl-8-(1H-pyrrol-1-yl)-2,3-dihydrocyclopenta[c]chromen-4(1H)-one **(6m)**: white solid; mp: 213.7-214.5 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.19 (s, 1H), 6.84 (t, *J* = 1.9 Hz, 2H), 6.44 (t, *J* = 1.9 Hz, 2H), 5.72 (s, 1H), 3.01 (t, *J* = 7.6 Hz, 2H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.41 (s, 3H), 2.20 (dd, *J* = 15.1, 7.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 156.3, 152.9, 151.4, 125.7, 124.8, 122.2, 119.7, 113.8, 112.1, 111.2, 32.2, 30.6, 22.7, 9.0; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{16}NO_3$ $[M + H]^+$, 282.1125; Found, 282.1120.

6-(2,5-dimethyl-1H-pyrrol-1-yl)-7-hydroxy-8-methyl-4-propyl-2H-chromen-2-one **(6w)**: white solid; mp: 191.1-192.0 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.28 (s, 1H), 6.19 (s, 1H), 6.00 (s, 2H), 5.71 (s, 1H), 2.65 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 1.97 (s, 6H), 1.74 – 1.62 (m, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.4, 156.3, 153.9, 153.2, 129.4, 121.8, 121.7, 113.9, 112.9, 111.7, 107.5, 34.1, 21.8, 14.1, 12.6, 8.9; HRMS: (*m/z*) *Anal.* Calcd for $C_{19}H_{22}NO_3$ $[M + H]^+$, 312.1594; Found, 312.1585.

6-(2,5-dimethyl-1H-pyrrol-1-yl)-3-ethyl-7-hydroxy-4,8-dimethyl-2H-chromen-2-one **(6x)**: white solid; mp: 216.5-217.1 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (s, 1H), 5.98 (s, 2H), 5.61 (s, 1H), 2.68 (dd, *J* = 14.6, 7.2 Hz, 2H), 2.39 (s, 3H), 2.34 (s, 3H), 1.97 (s, 6H), 1.15 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.8, 152.9, 151.4, 145.6, 129.4, 125.8, 121.8, 121.6, 114.3, 113.1, 107.3, 21.0, 14.8, 13.2, 12.5, 8.8; HRMS: (*m/z*) *Anal.* Calcd for $C_{19}H_{22}NO_3$ $[M + H]^+$, 312.1594; Found, 312.1588.

8-(2,5-dimethyl-1H-pyrrol-1-yl)-7-hydroxy-6-methyl-2,3-dihydrocyclopenta[c]chromen-4(1H)-one **(6y)**: white solid; mp: 172.2-173.1 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 (s, 1H), 5.94 (s, 2H), 5.75 (s, 1H), 3.00 (t, *J* = 7.6 Hz, 2H), 2.89 (t, *J* = 7.5 Hz, 3H), 2.40 (s, 3H), 2.25 – 2.15 (m, 2H), 1.96 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 156.3, 153.4, 153.3, 129.3, 125.4, 121.9, 121.7, 113.5, 112.3, 107.3, 32.2, 30.5, 22.6, 12.5, 9.0; HRMS: (*m/z*) *Anal.* Calcd for $C_{19}H_{20}NO_3$ $[M + H]^+$, 310.1438; Found, 310.1436.

The general procedure for preparing target compounds 6n-6v.

To a solution of compound **5** (1.0 mmol) (1.1 mmol, 1.1 equiv) in acetic acid (5.0 mL) was added substituted ethyl acetoacetates (1.1 mmol, 1.1 equiv). After stirring at 60 °C for 12 h, the mixture was poured into 40.0 mL ice water. The mixture was extracted with dichloromethane (3 × 20.0 mL). The extracts were dried over with Na_2SO_4 and the solvent was concentrated in vacuo. The crude product was purified by silica gel column chromatography (petroleum ether:ethyl acetate=10:1 to 4:1, v/v) to give the title compounds in 22%-78% yields (Table 1).

6-(2,5-dimethyl-1H-pyrrol-1-yl)-2H-chromen-2-one **(6n)**: white solid; mp: 171.0-171.6 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.08 (d, *J* = 9.6 Hz, 1H), 7.70 (s, 1H), 7.52 (s, 2H), 6.59 (d, *J* = 9.6 Hz, 1H), 5.82 (s, 2H), 1.98 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 153.2, 142.9, 135.5, 131.8, 129.0, 127.2, 119.3, 117.9, 117.8, 106.4, 13.1; HRMS: (*m/z*) *Anal.* Calcd for $C_{15}H_{14}NO_2$ $[M + H]^+$, 240.1019; Found, 240.1017.

6-(2,5-dimethyl-1H-pyrrol-1-yl)-4,7-dimethyl-2H-chromen-2-one **(6o)**: white solid; mp: 144.8-145.7 ℃; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.61 (s, 1H), 7.36 (s, 1H), 6.33 (s, 1H), 5.84 (s, 2H), 2.51 (d, *J* = 1.2 Hz, 3H), 1.99 (s, 3H), 1.89 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.7, 153.1, 152.0, 142.2, 134.7, 128.4, 124.8, 118.9, 118.8, 115.1, 106.1, 18.8, 17.6, 12.8; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{18}NO_2$ $[M + H]^+$, 268.1332; Found, 268.1336.

6-(2,5-dimethyl-1H-pyrrol-1-yl)-7-methyl-4-(trifluoromethyl)-2H-chromen-2-one **(6p)**: yellow solid; mp: 120.5-121.9 ℃; ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.67 (s, 1H), 7.37 (s, 1H), 7.11 (s, 1H), 5.86 (s, 2H), 2.50 (s, 3H), 1.97 (s, 3H), 1.85 (s, 6H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 158.1, 153.2, 143.2, 138.5 (q, *J* = 32.6 Hz), 134.5, 127.3, 124.2, 121.5 (q, *J* = 276.6 Hz), 119.3, 117.34 (q, *J* = 4.3 Hz), 111.7, 106.1, 16.9, 12.2; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{15}F_3NO_2$ $[M + H]^+$, 322.1049; Found, 322.1049.

4-(chloromethyl)-6-(2,5-dimethyl-1H-pyrrol-1-yl)-7-methyl-2H-chromen-2-one **(6q)**: white solid; mp: 132.7-133.3 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (s, 1H), 7.34 (s, 1H), 6.56 (s, 1H), 5.94 (s, 2H), 4.62 (s, 2H), 2.04 (s, 3H), 1.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.1, 153.3, 149.3, 142.8, 134.8, 128.3, 124.5, 119.1, 115.9, 115.7, 106.1, 41.1, 17.6, 12.7; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{17}ClNO_2$ $[M + H]^+$, 302.0942; Found, 302.0945.

6-(2,5-dimethyl-1H-pyrrol-1-yl)-7-methyl-4-propyl-2H-chromen-2-one **(6r)**: white solid; mp: 146.5-147.4 ℃; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.66 (s, 1H), 7.36 (s, 1H), 6.29 (s, 1H), 5.84 (s, 2H), 2.89 – 2.84 (m, 2H), 1.98 (s, 3H), 1.89 (s, 6H), 1.80 – 1.70 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, Acetone-d_6) δ 160.5, 156.8, 154.2, 142.6, 135.3, 128.5, 125.9, 119.3, 118.8, 114.4, 106.7, 34.0, 22.5, 17.3, 14.1, 12.7; HRMS: (*m/z*) *Anal.* Calcd for $C_{19}H_{22}NO_2$ $[M + H]^+$, 296.1645; Found, 296.1643.

6-(2,5-dimethyl-1H-pyrrol-1-yl)-3,4,7-trimethyl-2H-chromen-2-one **(6s)**: white solid; mp: 184.0-184.5 ℃; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.59 (s, 1H), 7.33 (s, 1H), 5.84 (s, 2H), 2.46 (s, 3H), 2.18 (s, 3H), 1.97 (s, 3H), 1.88 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 151.6, 145.6, 140.5, 134.5, 128.5, 124.6, 122.4, 119.4, 118.5, 105.9, 17.5, 15.3, 13.6, 12.8; HRMS: (*m/z*) *Anal.* Calcd for $C_{18}H_{20}NO_2$ $[M + H]^+$, 282.1489; Found, 282.1482.

6-(2,5-dimethyl-1H-pyrrol-1-yl)-3-ethyl-4,7-dimethyl-2H-chromen-2-one **(6t)**: white solid; mp: 146.8 -147.6 ℃; ^{1}H NMR (400 MHz, Acetone-d_6) δ 7.59 (s, 1H), 7.31 (s, 1H), 5.83 (s, 2H), 2.68 (q, *J* = 7.5 Hz, 2H), 2.49 (s, 3H), 1.97 (s, 3H), 1.88 (s, 6H), 1.12 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.5, 151.7, 145.1, 140.5, 134.5, 128.4, 128.2, 124.7, 119.5, 118.4, 105.9, 21.2, 17.4, 14.7, 13.1, 12.7; HRMS: (*m/z*) *Anal.* Calcd for $C_{19}H_{22}NO_2$ $[M + H]^+$, 296.1645; Found, 296.1644.

8-(2,5-dimethyl-1H-pyrrol-1-yl)-7-methyl-2,3-dihydrocyclopenta[c]chromen-4(1H)-one **(6u)**: white solid; mp: 200.6-201.3 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 7.29 (s, 1H), 5.90 (s, 2H), 3.05 (t, *J* = 7.6 Hz, 2H), 2.91 (t, *J* = 7.4 Hz, 2H), 2.28 – 2.17 (m, 2H), 2.01 (s, 3H), 1.91 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.8, 155.5, 153.4, 140.8, 134.3, 128.1, 127.9, 124.6, 118.3, 117.3, 105.7, 31.9, 30.6, 22.4, 17.5, 12.5; HRMS: (*m/z*) *Anal.* Calcd for $C_{19}H_{20}NO_2$ $[M + H]^+$, 294.1489; Found, 294.1489.

3-chloro-6-(2,5-dimethyl-1H-pyrrol-1-yl)-4,7-dimethyl-2H-chromen-2-one **(6v)**: white solid; mp: 174.5-175.7 ℃; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.32 (s, 1H), 5.95 (s, 2H), 2.55 (s, 3H), 2.03 (s, 3H), 1.92 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.9, 150.9, 147.4, 142.2, 135.3, 128.3, 125.1, 121.0, 118.8, 118.6, 106.2, 17.6, 16.3, 12.7; HRMS: (*m/z*) *Anal.* Calcd for $C_{17}H_{17}ClNO_2$ $[M + H]^+$, 302.0942; Found, 302.0948.

Biological assay. The *in vitro* fungicidal activity of the target compounds was evaluated based on the mycelium growth rate method against six phytopathogenic fungi *Botrytis cinerea*, *Alternaria solani*, *Rhizoctorzia solani*, *Alternaria leaf spot*, *Gibberella zeae* and *Cucumber anthrax*. After retrieval from the storage tube, the strains were incubated in Potato Dextrose Agar at 25℃ for one week to get new mycelia for the antifungal assay. All the target compounds were dissolved in N, N-dimethylformamide (5.0 mL) to generate a 100 ppm stock solution. The tested solutions were prepared by diluting the above solution.

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Conflict of interest

The authors declare that they have no conflict of interest.

Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of this article.

Keywords: Coumarin • Pyrrole • Synthesis • Antifungal activity •

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Layout 2:

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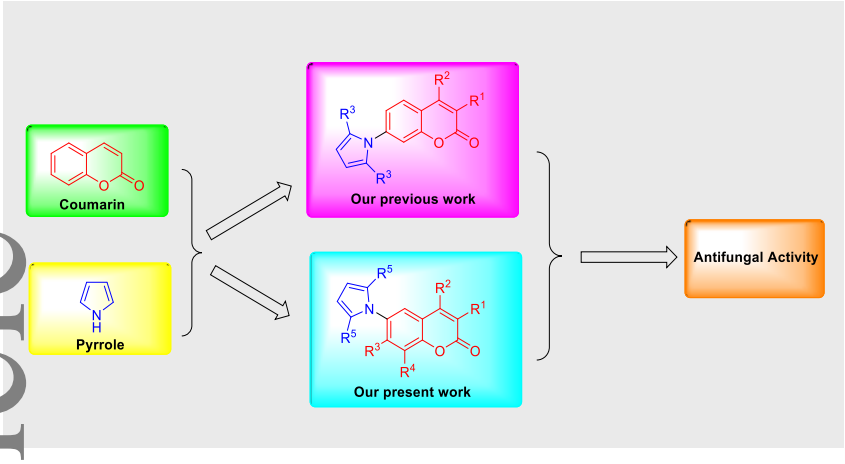

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Design, Synthesis, and Antifungal Evaluation of Novel Coumarin-Pyrrole Hybrids