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Design, Synthesis and Biological Evaluation of *N*-((2-phenyloxazol-4-yl)methyl) Pyrimidine Carboxamide Derivatives as Potential Fungicidal Agents

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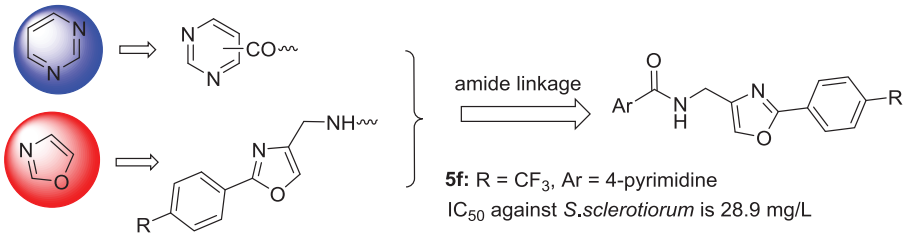

Abstract: Twelve N-((2-phenyloxazol-4-yl)methyl) pyrimidine carboxamide derivatives were designed, synthesized, and characterized by ^{1}H NMR, ^{13}C NMR, and HRMS. The fungicidal activities of these new compounds against *Sclerotinia sclerotiorum, Botrytis cinereal*, and *Colletotrichum fragariae* were evaluated. The results indicated that compounds **5b**, **5f**, and **5g** displayed potential fungicidal activities against tested fungi, especially **5f** exhibited IC_{50} value of 28.9 mg/L against *S. sclerotiorum*. Moreover, the compounds **5f** and **5g** showed IC_{50} values of 54.8 mg/L and 62.2 mg/L against *C. fragariae* respectively, which shows that they were more active than the commercial fungicide hymexazol. The superficial structure-activity relationships were discussed, which may be of benefit for the development of fungicides and discovery of novel fungicides.

Keywords: Oxazole derivative, Synthesis, Fungicidal activities, Structure-activity relationship

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Introduction

Plant diseases are one of the main causes of crops reduction, around 80% of which result from fungi infections [1,2]. Furthermore, human health is harmed because of the mycotoxins that are produced by the fungi [3,4]. Undoubtedly, rational application of fungicides is an effective method for fungal control. However, most fungi have developed resistances or cross-resistances to the commercial fungicides [5]. Therefore, development and discovery of novel fungicides with high-efficiency and lower toxicity is tremendously necessary and needed with great urgency.

The oxazole skeleton is of extraordinary importance in the design of active fungicidal molecules. Recently, lots of oxazole derivatives with potential fungicidal activity have been discovered [6-9]. Studies suggest that the oxazole derivatives display a broad spectrum of antifungal activity. Moreover, there are many oxazole derivatives being developed for the commercial fungicides (Figure 1a), such as famoxadone [10], hymexazol [11], and oxadixyl [12]. On the other hand, the pyrimidine ring is a remarkable moiety in various bioactive molecules including antifungal, antimicrobial, anticancer and anti-inflammatory agents [13]. In particular, pyrimidine derivatives hold a pivotal position in the structure of fungicides design,

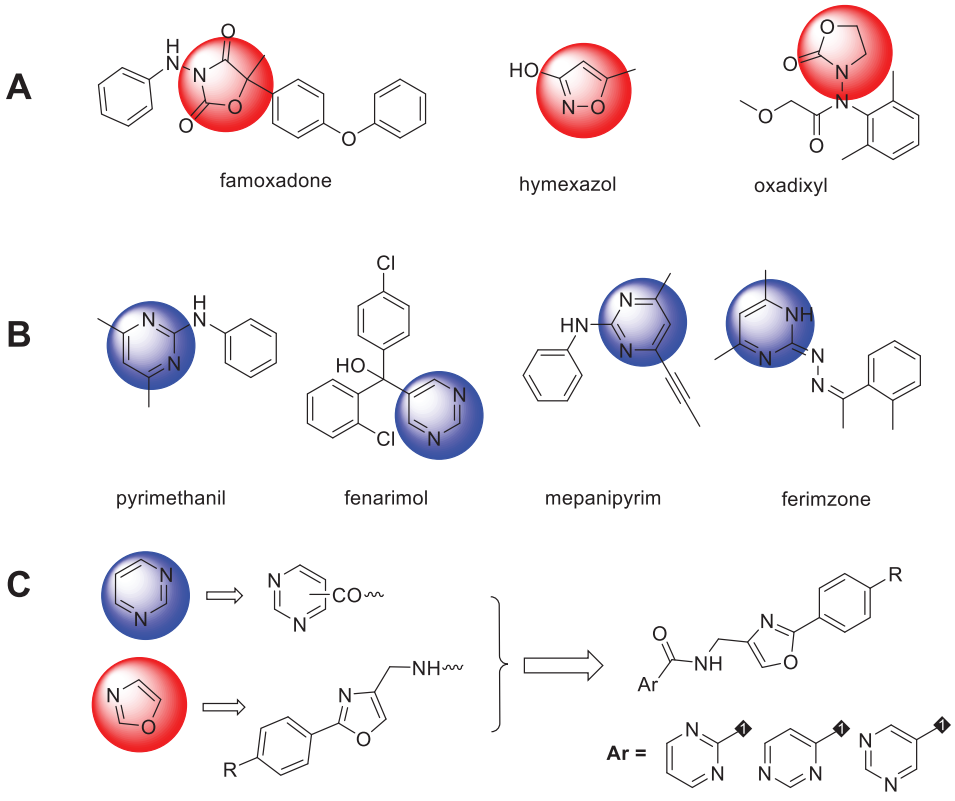


Figure 1 The design of fungicidal 2-aryl-oxazole derivatives containing pyrimidine

and have yielded the commercial products of pyrimethanil [14], fenarimol [15], mepanipyrim [16], and ferimzone [17] (Figure 1b). Literature showed that the introduction of a pyrimidine fragment was beneficial to the improvement of fungicidal activities of compounds [18-20]. Toshihiro et al. [21] gave the systematic structure-activity relationship (SAR) of pyrimidine derivatives. They found that the pyrimidine ring introduced the same substituents at the different positions and influenced the bioactivities of the compounds remarkably. Inspired by this work, formamide derivatization on different positions of pyrimidine was considered in our design strategy. In our effort to seek novel compounds with potential fungicidal activities, we tried to use a molecular hybridization strategy to combine the active fragment oxazole and pyrimidine via an amido bond (Figure 1c), in which R was chosen as a hydrogen atom, methyl, methoxyl, or trifluoromethyl and Ar was fixed as 2 - pyrimidinyl, 4 – pyrimidinyl or 5 – pyrimidinyl. Herein, we report the synthesis of 12 pyrimidine amide derivatives containing 2-phenyl-oxazole and their fungicidal activities against three fungi, *Sclerotinia sclerotiorum*, *Botrytis cinereal*, and *Colletotrichum fragariae*, which are known as the main pathogenic fungi in agriculture. Furthermore, the apparent SAR of these compounds were discussed.

Result and discussion

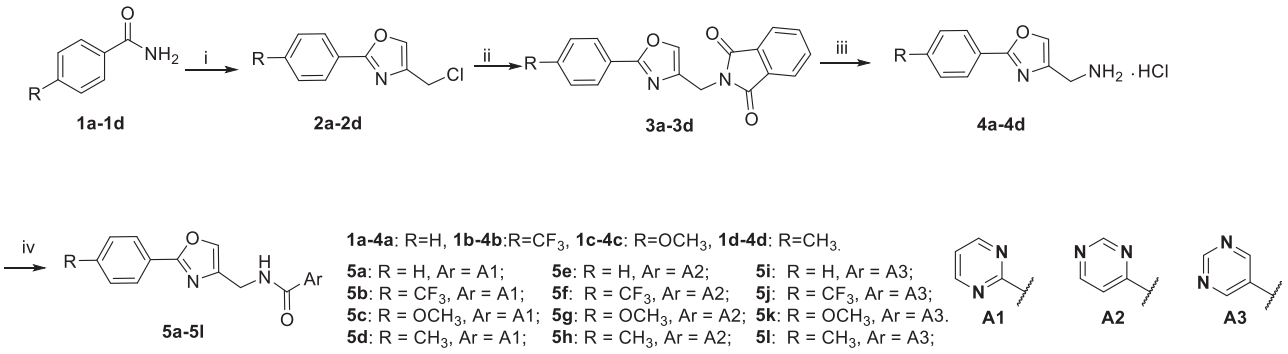
The target compounds, *N*-((2-(4-substituted-phenyl)oxazol-4-yl)methyl)pyrimidine carboxamides (**5a-5l**) were synthesized as outlined in Scheme 1. Initially, the skeleton of the oxazole ring was built by a Bredereck reaction [22]. The 2-aryl-4-chloromethyl oxazole (**2a-2d**) was obtained via reaction between 1,3-dichloroacetone and amide (**1a-1d**) and heating at 130 °C. The Gabriel reaction [23] was carried out to shift **2a-2d** to the key intermediates **4a-4d.** In brief, potassium phthalimide was reacted with the corresponding 4-chloromethyl oxazole (**2a-2d**) in *N*,*N*-dimethylformamide (DMF) at 80 °C. Then, these synthesized phthalimide derivates (**3a-3d**) were further treated with hydrazine hydrate in ethanol at reflux temperature to result in the corresponding (2-aryl-oxazol-4-yl)methanamine. Afterwards, amine hydrochloride derivatives **4a-4d** were generated by addition of concentrated hydrochloric acid to (2-aryl-oxazol-4-yl) methanamine.

Finally, condensation reaction between **4a-4d** and pyrimidine carboxylic acid was carried out in the presence of 2-(7-Azabenzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HATU) to obtain target compounds **5a-5l**, whose structures were identified by ^{1}H

NMR, ^{13}C NMR, and HRMS as detailed in the experimental section. The final step of the synthesis gave satisfactory yields (≥ 80%) and the overall yield of the synthesis route reported here was over 50%, which demonstrated that the synthesis pathway shown in **Scheme 1** is reasonable and available.

The structures and fungicidal activities against *S. sclerotiorum*, *B. cinereal*, and *C. fragariae* were shown in Table 1. All target compounds were screened at three concentrations including 100 mg/L, 50 mg/L, and 30 mg/L. As a result, **5f** and **5g** showed better fungicidal activities against the three test fungi (Figure 2). In detail, for *S. sclerotiorum*, **5f**, **5g**, **5j** displayed over 60% inhibition rate at the concentration of 100 mg/L. In particular, **5f** displayed 45.6% inhibition rate against *S. sclerotiorum* at 30 mg/L, while **5g** and **5j** showed less activities (13.0% and 28.7%) at the equivalent concentration. On the other hand, **5f** and **5g** exhibited over 50% inhibition against *B. cinerea* at 100 mg/L. In addition, **5f** and **5g** showed similar effects against *C. fragariae* to the commercial product hymexazol. Finally, as shown in Table 2, the IC_{50} values of the better bioactive compounds (**5b**, **5f** and **5g**) were given. It revealed that **5f** (54.8 mg/L) and **5g** (62.2mg/L) display lower IC_{50} value against *C. fragariae* than that of hymexazol (148.9mg/L).

The superficial structure-activity relationship presented a general trend. On the basis of the bioassay data, the substituents R and Ar reflected a momentous relationship with the activities. When Ar remained constant, the influence of R on the fungicidal activities showed a regular change. The fungicidal activities of target compounds is enhanced when the R is a CF_3 rather than any other substituent. Taking the assay concentration of 100 mg/L for example, compound **5f** (75.6% inhibition rates) is more active than **5e** (69.1% inhibition rates), **5g** (39.1% inhibition rates), or **5h** (no effect) against *S. sclerotiorum*. Ordinarily,



Scheme 1 Synthesis The synthesis route of a compound library based on oxazole derivatives as building blocks **5a-5i**. Reagents and conditions: i) 1,3-dichloroacetone, neat, 130 °C; ii) Potassium phthalimide, DMF, 80 °C; iii) Hydrazine hydrate, EtOH, reflux, then 37% HCl, rt; iv) Pyrimidine carboxylic acid, HATU, Et_3N, DMAP, DCM, 0 °C and then room temperature

Table 1 Inhibition ratio(%) of compounds **5a-5l** and hymexazol against *S. sclerotiorum*, *B. cinerea*, and *C. fragariae*

Compound	Ar	R	*S. Sclerotiorum* (mg/L)			*B. Cinerea* (mg/L)			*C. Fragariae* (mg/L)		
			30	50	100	30	50	100	30	50	100
5a	A1	H	-[a]	-	-	-	5.80	12.56	-	19.59	19.92
5b	A1	CF_3	-	4.78	5.22	13.04	18.36	38.65	20.27	29.73	43.24
5c	A1	OCH_3	-	4.78	5.22	-	2.42	3.86	10.14	13.51	25.00
5d	A1	CH_3	-	3.7	10.0	-	6.8	7.9	-	-	6.3
5e	A2	H	3.04	18.26	39.13	10.14	18.84	27.05	12.16	14.86	24.32
5f	A2	CF_3	45.65	66.09	75.65	38.16	49.76	53.14	29.05	45.27	57.43
5g	A2	OCH_3	13.04	67.83	69.13	10.63	31.40	51.69	23.65	48.65	52.03
5h	A2	CH_3	-	19.8	17.2	13.3	17.2	28.6	16.3	22.9	30.8
5i	A3	H	-	19.13	34.78	-	6.76	7.73	10.14	10.81	13.51
5j	A3	CF_3	28.70	50.87	62.17	16.91	9.18	29.95	10.81	17.57	37.16
5k	A3	OCH_3	-	12.17	28.26	4.35	3.38	8.70	18.92	17.57	21.62
5l	A3	CH_3	-	8.9	4.9	-	-	14.8	-	-	-
6[b]			88.5	92.8	100	72.4	78.9	82.2	38.8	36.9	44.6

[a]means no effect. [b]Hymexazol.

Table 2 IC_{50} values of the target compounds against *S. sclerotiorum*, *B. cinerea*, and *C. fragariae*

Compound	*S. sclerotiorum*			*B. cinerea*			*C. fragariae*		
	IC_{50} (mg/L)	Regression equation	R^2	IC_{50} (mg/L)	Regression equation	R^2	IC_{50} (mg/L)	Regression equation	R^2
5b	92.6	y=0.0061x +0.1139	0.780	146.0	y=0.0038x +0.0378	0.992	118.8	y=0.004xc +0.0968	0.971
5f	28.9	y=0.0073 +0.1792	0.845	51.7	y=0.0051x +0.1596	0.755	54.8	y=0.0049x +0.1851	0.941
5g	40.0	y=0.0065x +0.1533	0.654	116.8	y=0.004x +0.0664	0.459	62.2	c0.0053x +0.116	0.832
Hymexazol	10.4	y=0.0072x +0.4217	0.642	4.4	y=0.003x +0.575	0.774	148.9	y=0.0038x +0.0619	0.908

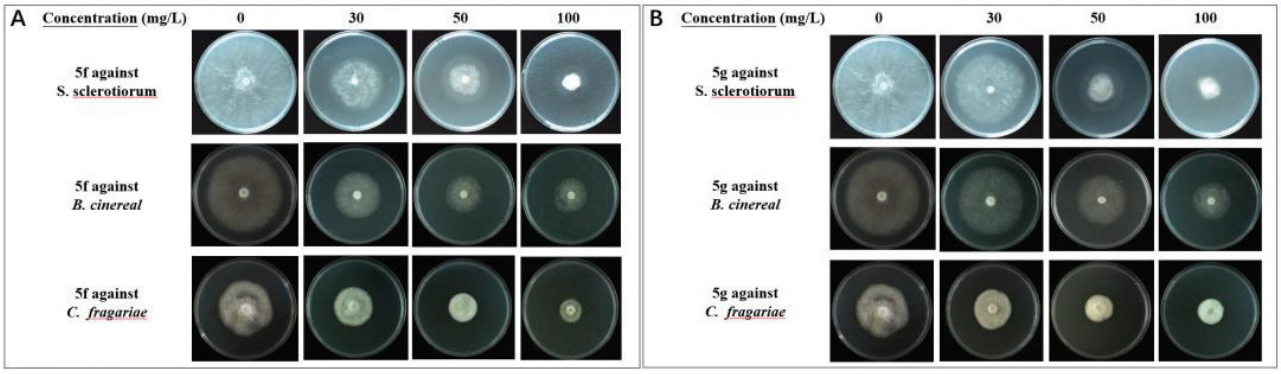


Figure 2 The fungicidal efficacy of **5f** and **5g**

the influence of R on improved activity may be concluded as follows: CF_3 > OCH_3 > H > CH_3. In addition, when R is kept invariant, modification of the Ar moiety from A3 and A1 to A2 group increased the fungicidal activity evidently. For example, the fungicidal activities against *S. sclerotiorum* are correlated as follows: **5e** > **5i** > **5a**, **5f** > **5j** > **5b**, and **5g** > **5h** > **5c**.

Conclusion

In this paper, we synthesized and investigated *N*-((2-phenyloxazol-4-yl)methyl) pyrimidine carboxamide derivatives *in vitro* for their fungicidal activities against three fungi, namely *S. sclerotiorum*, *B. Cinerea*, and *C. fragariae*. It was noted that compounds **5f** and **5g** showed fungicidal activities against these three fungi. Especially, **5f** and **5g** displayed lower IC_{50} values than hymexazol (a positive control) against *C. fragariae*. With these findings, the apparent structure–activity relationships were discussed. Our current study indicated that the present target compounds should be worthwhile for further study as the lead compounds in the search for discovering potential fungicides.

Experimental Section

Synthesis and characterization

Melting points (m.p.) were measured on a MP450 melting-point apparatus (Shandong Nanon Instrument LTD, CITY, China). The NMR spectra were recorded on a Bruker AV-500 spectrometer (Bruker, Karlsruhe, Germany) with TMS as an internal standard. HRESIMS was measured by a Shimazu LC-20AD AB SCIEX triple TOF 5600+ MS spectrometer (Shimadzu Corporation, Tokyo, Japan). Column chromatography was performed using 200-300 mesh silica gels. The solvents and reagents were dried prior to use. The general synthetic methods for compounds **5a**-**5l** are detailed in Scheme 1 and brief procedures are shown below. Each target compound was identified and verified by ^{1}H NMR, ^{13}C NMR, and HRESIMS.

Synthesis of 4-(chloromethyl)-2-arlyloxazole (2a) and its analogues (2b-2d)

A mixture of benzamide (1.81 g, 15 mmol) and 1,3-dichloroacetone (1.9 g, 17 mmol) was ground thoroughly. Then

the mixture was heated to liquation and the reaction temperature was kept at 130 °C for 4 h. Once cooled to room temperature, 150 mL EA was poured into the product and it was washed twice with saturated Na_2CO_3 solution. The EA layer was dried over Na_2SO_4, filtered and evaporated. The residue was purified by chromatography on a silica gel column using petroleum ether (PE) and ethyl acetate (EA) as the eluents to afford **2a** as a white powder 2.6 g (90% yield). The analogues **(2b-2d)** could be synthesized by the method similar to that described in the synthesis of **2a.**

4-(Chloromethyl)-2-phenyloxazole (2a): White solid; 90% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.02 (dd, J = 6.7, 3.0 Hz, 2H), 7.67 (s, 1H), 7.58 – 7.35 (m, 3H), 4.56 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.3, 138.8, 136.2, 130.7, 128.8, 127.0, 126.5, 37.1.

4-(Chloromethyl)-2-(4-(trifluoromethyl)phenyl) oxazole (2b): White solid; 85% yield;^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.1 Hz, 2H), 7.76 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 4.59 (d, J = 0.8 Hz, 2H).^{13}C NMR (125 MHz, $CDCl_3$) δ 160.9, 139.3, 136.9, 132.31 (q, J = 32.7 Hz), 130.1, 126.8, 125.85 (q, J = 3.8 Hz), 124.8, 122.7, 36.8.

4-(Chloromethyl)-2-(4-methoxyphenyl)oxazole (2c): White solid; 87% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.10 – 7.87 (m, 1H), 7.66 (t, J = 0.8 Hz, 1H), 7.08 – 6.79 (m, 1H), 4.57 (d, J = 0.9 Hz, 2H), 3.86 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 162.5, 161.6, 138.5, 135.6, 128.2, 119.8, 114.2, 55.4, 37.2.

4-(Chloromethyl)-2-(p-tolyl)oxazole (2d): White solid; 92% yield; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (d, J = 8.2 Hz, 2H), 7.68 (s, 1H), 7.26 (d, J = 8.0 Hz, 2H), 4.57 (d, J = 0.7 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.6, 141.1, 138.6, 135.9, 130.0, 129.5, 129.3, 126.5, 124.3, 37.2, 21.5.

Synthesis of 4-(aminomethyl)-2-arlyl oxazole (4a) and its analogues (4b- 4d)

To a solution of **2a** (2.6 g, 13.5 mmol) in 30 mL DMF was added potassium phthalimide (3.0g, 16.2mmol) in portions. After the mixture was stirred at 80 °C for 5 h, the mixture was poured into ice water and the precipitate was collected by filtration and washed with water. **3a** was obtained as blown solid. Then **3a** was mixed with 150 mL ethanol and hydrazine hydrate (50%, 5.2 g, 53.0 mmol). After 5 h under reflux, the precipitate was separated by filtration and the solvent of filtrate was removed under reduced pressure. The mixture was poured into ice water and the aqueous phase was extracted with EA. The organic layer was washed twice with water and dried over Na_2SO_4, filtered, and concentrated under reduced pressure to obtain blown oil. Then the oil was dissolved in 10 mL acetone, then added 0.5 mL concentrated hydrochloric acid to precipitate a large amount of solid. The precipitate was separated by filtration and washed twice with 20 mL acetone, dried in vacuum to afford **4a** as white solid (2.4 g, 88% yields for two steps). The analogues (**4b**-4**d**) could be synthesized by the method similar to that described in the synthesis of **4a.**

(2-Phenyloxazol-4-yl)methanamine hydrochloride (4a): White solid; 88% yield; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.59 (s, 3H), 8.30 (s, 1H), 8.09 – 7.87 (m, 2H), 7.66 – 7.41 (m, 3H), 4.03 (d, J = 0.8 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.4, 138.8, 135.8, 131.5, 129.8, 126.9, 126.4, 34.7.

(2-(4-(Trifluoromethyl)phenyl)oxazol-4-yl)methanamine hydrochloride (4b): Brown solid; 73% yield ;^{1}H NMR (600 MHz, DMSO-d_6) δ 8.68 (s, 3H), 8.40 (s, 1H), 8.19 (d, J = 8.1 Hz, 2H), 7.94 (d, J = 8.3 Hz, 2H), 4.05 (q, J = 5.7 Hz, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 160.0, 139.7, 136.2, 131.07 (q, J = 32.0 Hz), 130.4, 127.2, 126.80 (q, J = 3.6 Hz), 124.32 (q, J = 272.3 Hz), 34.6.

(2-(4-Methoxyphenyl)oxazol-4-yl)methanamine hydrochloride (4c): White solid; 85% yield; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.59 (s, 3H), 8.21 (s, 1H), 8.08 – 7.81 (m, 2H), 7.13 – 7.04 (m, 2H), 3.99 (s, 2H), 3.83 (s, 3H).^{13}C NMR (150 MHz, DMSO-d_6) δ 161.8, 161.5, 138.0, 135.5, 128.2, 119.5, 115.2, 55.9, 34.7.

(2-(*p*-Tolyl)oxazol-4-yl)methanamine hydrochloride (4d): White solid; 82% yield; ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.58 (brs, 3H), 8.25 (s, 1H), 7.88 (d, J = 8.2 Hz, 2H), 7.38 (d, J = 8.0 Hz, 2H), 4.01 (s, 2H), 2.38 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 161.6, 141.4, 138.4, 135.6, 130.3, 126.4, 124.3, 34.7, 21.5.

Synthesis of *N*-((2-phenyloxazol-4-yl)methyl)pyrimidine-2-carboxamide (5a) and its analogues (5b-5i)

To a solution of pyrimidine-2-carboxamide (58.5 mg, 0.48 mmol), Et_3N (202 mg, 2.0 mmol), HATU (273.6 mg, 0.72 mmol) and 4-dimethylaminopyridine (DMAP, 87.8 mg, 0.72 mmol) in 10 mL dichloromethane (DCM), **4a** (100 mg, 0.48 mmol) was added under 0–5 °C and kept stirring for 30 minutes. Then the mixture was stirred at ambient temperature for 5 h. The reaction mixture was poured into saturated NH_4Cl aqueous solution (10 mL). The organic layer was washed twice with 5 mL saturated sodium chloride solution and dried over Na_2SO_4 and evaporated. The residue was recrystallized from ethanol to afford **5a** as a white powder (123.6 mg, 92% yield). The derivatives (**5b**-**5i**) could be synthesized by the method similar to that described in the synthesis of **5a.**

***N*-((2-phenyloxazol-4-yl)methyl)pyrimidine-2-carboxamide (5a):** White solid; 92% yield; m.p. 145 - 146 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, J = 4.9 Hz, 2H), 8.07 – 8.00 (m, 3H), 7.72 (s, 1H), 7.46 – 7.43 (m, 3H), 4.69 (d, J = 5.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 162.1, 157.5, 157.5, 138.2, 135.8, 130.5, 128.8, 127.3, 126.4, 122.6, 35.9. HRMS *m/z* calcd for $C_{15}H_{12}N_4O_2$ (M-H)$^-$ 279.0887; Found 279.0887.

***N*-((2-(4-(trifluoromethyl)phenyl)oxazol-4-yl)methyl)pyrimidine-2-carboxamide (5b):** White solid; 90% yield ; m.p. 139 - 140 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.89 (d, J = 4.9 Hz, 2H), 8.15 (d, J = 8.2 Hz, 2H), 7.78 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 7.46 (t, J = 4.9 Hz, 1H), 4.70 (d, J = 5.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 160.6, 157.5, 157.5, 138.8, 136.7, 126.7, 130.4, 25.9, 125.8, 122.7, 35.8. HRMS *m/z* calcd for $C_{16}H_{11}F_3N_4O_2$ (M-H)$^-$ 347.0761; Found 347.0759.

***N*-((2-(4-methoxyphenyl)oxazol-4-yl)methyl)pyrimidine-2-carboxamide (5c):** White solid; 93% yield; m.p. 59 - 60 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.88 (d, J = 4.8 Hz, 2H), 7.96 (d, J = 8.7 Hz, 2H), 7.67 (s, 1H), 7.45 (d, J = 4.8 Hz, 1H), 6.96 (d, J = 8.7 Hz, 2H), 4.66 (d, J = 5.7 Hz, 3H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.3, 162.2, 161.5, 157.5, 157.5, 137.9, 135.2, 128.1, 122.6, 120.1, 114.2, 76.8, 55.4, 35.9. HRMS *m/z* calcd for $C_{16}H_{14}N_4O_3$ (M-H)$^-$ 309.0993; Found 309.0991.

***N*-((2-(p-tolyl)oxazol-4-yl)methyl)pyrimidine-2-carboxamide (5d):** White solid; 89% yield; m.p. 170-172°C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.30 (t, J = 5.9 Hz, 1H), 8.98 (d, J = 4.9 Hz, 2H), 8.01 (s, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.70 (t, J = 4.9 Hz, 1H), 7.34 (d, J = 8.0 Hz, 2H), 4.47 (dd, J = 6.0, 0.9 Hz, 2H), 2.37 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.9, 161.2, 158.4, 158.2, 141.0, 139.7, 136.6, 130.2, 126.3, 124.7, 123.5, 35.9, 21.5. HRMS *m/z* calcd for $C_{16}H_{14}N_4O_2$ (M-H)$^-$ 293.1044; Found 293.1040.

***N*-((2-phenyloxazol-4-yl)methyl)pyrimidine-4-carboxamide (5e):** White solid; 90% yield; ; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (d, J = 1.2 Hz, 1H), 8.98 (d, J = 5.0 Hz, 1H), 8.49 (brs, 1H), 8.14 (dd, J = 5.0, 1.3 Hz, 1H), 8.09 – 7.99 (m, 2H), 7.70 (s, 1H), 7.53 – 7.36 (m, 4H), 4.65 (d, J = 5.8 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 162.2, 159.2, 157.9, 156.0, 138.0, 135.6, 130.6, 128.8, 127.2, 126.4, 118.6, 35.6. HRMS *m/z* calcd for $C_{15}H_{12}N_4O_2$ (M-H)$^-$ 279.0887; Found 279.0886.

***N*-((2-(4-(trifluoromethyl)phenyl)oxazol-4-yl)methyl)pyrimidine-4-carboxamide (5f):** White solid; 90% yield; m.p. 122 - 124 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26 (d, J = 1.0 Hz, 1H), 8.99 (d, J = 5.0 Hz, 1H), 8.53 (s, 1H), 8.16 – 8.13 (m, 3H), 7.76 (s, 1H), 7.72 (d, J = 8.3 Hz, 2H), 4.67 (d, J = 5.9 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.8, 160.7, 159.3, 157.9, 155.9, 138.6, 136.4, 132.14 (q, J = 32.7 Hz), 130.3, 126.7, 125.83 (q, J = 3.8 Hz), 123.76 (d, J = 272.4 Hz), 118.6, 35.5. HRMS *m/z* calcd for $C_{16}H_{11}F_3N_4O_2$ (M-H)$^-$ 347.0761; Found 347.0758.

***N*-((2-(4-methoxyphenyl)oxazol-4-yl)methyl)pyrimidine-4-carboxamide (5g):** White solid; 87% yield; m.p. 127 - 129 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (d, J = 1.2 Hz, 1H), 8.98 (d, J = 5.0 Hz, 1H), 8.48 (brs, 1H), 8.13 (dd, J = 5.0, 1.3 Hz, 1H), 8.07 – 7.87 (m, 2H), 7.65 (s, 1H), 7.08 – 6.79 (m, 2H), 4.63 (d, J = 5.8 Hz, 2H), 3.86 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.7, 162.3, 161.5, 159.2, 157.8, 156.1, 137.8, 135.1, 128.1, 120.0, 118.6, 114.2, 55.4, 35.7. HRMS *m/z* calcd for $C_{16}H_{14}N_4O_3$ (M-H)$^-$ 309.0993; Found 309.0989.

***N*-((2-(p-tolyl)oxazol-4-yl)methyl)pyrimidine-4-carboxamide (5h):** White solid; 80% yield; m.p. 157-159 °C ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.30 (t, J = 5.9 Hz, 1H), 8.97 (d, J = 4.9 Hz, 2H), 8.00 (s, 1H), 7.84 (d, J = 8.2 Hz, 2H), 7.69 (t, J = 4.9 Hz, 1H), 7.33 (d, J = 8.0 Hz, 2H), 4.46 (dd, J = 6.0, 0.8 Hz, 2H), 2.35 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 162.9, 161.2, 158.3, 158.2, 141.0, 139.7, 136.6, 130.2, 126.3, 124.7, 123.6, 35.9, 21.5. HRMS *m/z* calcd for $C_{16}H_{14}N_4O_2$ (M-H)$^-$ 293.1044; Found 293.1047.

***N*-((2-phenyloxazol-4-yl)methyl)pyrimidine-5-carboxamide (5i):** White solid; 83% yield; m.p. 134 - 136 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 9.16 (s, 1H), 8.00 (dd, J = 6.6, 2.9 Hz, 2H), 7.73 (s, 1H), 7.47 (dd, J = 4.9, 1.6 Hz, 3H), 7.22 (s, 1H), 4.63 (d, J = 5.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3, 162.4, 160.6, 155.7, 137.5, 135.8, 130.8, 128.9, 127.6, 126.9, 126.4, 35.7. HRMS *m/z* calcd for $C_{15}H_{12}N_4O_2$ (M-H)$^-$ 279.0887; Found 279.0887.

***N*-((2-(4-(trifluoromethyl)phenyl)oxazol-4-yl)methyl)pyrimidine-5-carboxamide (5j):** White solid; 81% yield; m.p. 170 - 172 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 9.16 (s, 2H), 8.11 (d, J = 8.2 Hz, 3H), 7.77 (s, 1H), 7.71 (d, J = 8.3 Hz, 3H), 7.19 (brs, 1H), 4.64 (d, J = 5.4 Hz, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 160.9, 160.7, 155.7, 138.1, 136.6, 132.37 (d, J = 32.8 Hz), 130.1, 127.5, 126.7, 126.0, 125.9 (q, J = 3.7 Hz), 123.71 (d, J = 272.3 Hz), 35.8. HRMS *m/z* calcd for $C_{16}H_{11}F_3N_4O_2$ (M-H)$^-$ 347.0761; Found 347.0759.

***N*-((2-(4-methoxyphenyl)oxazol-4-yl)methyl)pyrimidine-5-carboxamide (5k):** White solid; 83% yield; m.p. 166 – 167 °C ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.27 (s, 1H), 9.15 (s, 2H), 7.89 (d, J = 8.9 Hz, 2H), 7.63 (s, 1H), 7.51 (s, 1H), 6.93 (d, J = 8.9 Hz, 2H), 4.57 (d, J = 5.3 Hz, 2H), 3.83 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 162.7, 162.0, 160.9, 156.2, 137.7, 135.6, 128.4, 128.0, 120.1, 114.7, 55.8, 39.0, 36.2. HRMS *m/z* calcd for $C_{16}H_{14}N_4O_3$ (M-H)$^-$ 309.0993; Found 309.0991.

***N*-((2-(p-tolyl)oxazol-4-yl)methyl)pyrimidine-5-carboxamide (5l):** White solid; 89% yield; m.p. 158 - 159 °C ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.38 (t, J = 5.5 Hz, 0H), 9.32 (s, 0H), 9.20 (s, 1H), 8.11 (s, 1H, 7.85 (d, J = 8.2 Hz, 1H), 7.33 (d, J = 8.0 Hz, 1H), 4.54 – 4.37 (m, 2H), 2.36 (s, 3H). ^{13}C NMR (150 MHz, DMSO-d_6) δ 163.6, 161.3, 160.5, 156.4, 141.0, 139.5,

136.9, 130.2, 128.1, 126.3, 124.7, 36.0, 21.5. HRMS *m/z* calcd for $C_{16}H_{14}N_4O_2$ $(M\text{-}H)^-$ 293.1044; Found 293.1042.

Antifungal assay

The antifungal activities of the above compounds against *S. sclerotiorum*, *B. cinerea*, and *C. fragariae* were tested by the method described in the literature [24]. Briefly, 0.5 mL mycelial plugs of the pathogens were prepared and transferred into PDA plates supplemented with indicated concentration of the compounds, respectively. The same volumes of DMSO were used as a control and all the plates were incubated at room temperature and the growth rate was evaluated by the colony diameters in triplicate. The experiment was repeated thrice. The inhibition rate of the test compounds against three fungi was calculated by the below formula, where *C* represents the diameter of fungi growth on untreated PDA, *T* represents the diameter of fungi on treated PDA, and *I* is the inhibition rate.

$$I\,(\%) = [(C - T) / (\text{C-0.4})] \times 100\%.$$

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