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Design, synthesis and antifungal evaluation of novel pyrazole carboxamides with diarylamines scaffold as potent succinate dehydrogenase inhibitors

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ABSTRACT

Sixteen novel pyrazole carboxamides with diarylamines scaffold were designed, synthesized and characterized in detail via ^{1}H NMR, ^{13}C NMR and ESI-HRMS. Preliminary bioassays showed that some of the target compounds exhibited good antifungal activity against *Rhizoctonia solani*, *Fusarium oxysporum*, *Phytophthora infestans* and *Fusarium graminearum*. Among them, compound **1c** exhibited the highest antifungal activities against *R. solani in vitro* with EC_{50} value of 0.005 mg/L, superior to the commercially available fungicide fluxapyroxad (EC_{50} = 0.033 mg/L). And compound **1c** (IC_{50} = 0.034 mg/L) showed higher inhibition abilities against succinate dehydrogenase than fluxapyroxad (IC_{50} = 0.037 mg/L). This study suggests that compound **1c** could be regarded as a potential succinate dehydrogenase inhibitor.

Succinate dehydrogenase (SDH, EC 1.3.5.1, also known as complex II), which catalyzes the oxidation of succinate to fumarate in the mitochondrial matrix, is the only enzyme complex simultaneously involved in the respiration chain and Krebs cycle.[1–3] Due to its crucial role in life processes, SDH has been particularly appreciated as a promising target for agrochemical discovery.[4–6] To date, 19 structurally diverse SDH inhibitor (SDHI) fungicides have been successfully developed and shown potential for plant protection. As one of the most important categories of the SDHIs, the substituted pyrazole carboxamide fungicides have been intensively employed throughout the world to fight again slightly destructive plant pathogens, such as *Botrytis cinerea*, *Sclerotinia* spp., *Leveillula taurica* and *Sphaerotheca macularis*.[7] They share a prototypical pharmacophoric scheme, which consists of a substituted pyrazole carboxyl "core", a conserved amide function and an amine moiety (Fig.1).[8] According to the cocrystal structure of the SDH from porcine heart,[9] avian,[10] and *Escherichia coli*,[11] the substituted pyrazole carboxyl "core" buries deep into the ubiquinone binding site (Q-site) and contributes predominantly to the binding affinity of SDHI fungicides. So lots of companies, institutes and universities have carried on the substantial work. They kept the substituted pyrazole carboxyl "core" and amide function unchanged, and the amine moieties have been structurally diverse. For example, Yang et al. discovered if the biphenyl group in bixafen was replaced with the diphenyl ether group, the novel substituted pyrazole carboxamide fungicides showed good antifungal activities.[12]

Many bioactive compounds with diarylamines have been used in the agrochemical field over the years.[13] Diarylamine derivatives feature significant biological activities, including fungicidal, insecticidal, acaricidal, rodenticidal and herbicidal activities.[14–18] Therefore, diarylamine may represent a promising bioactive moiety to integrate with other pharmacophore. Recently our research group discovered when the phenyl group in fenfuram (a commercial fungicide) was replaced with the diarylamine, the novel fenfuram-diarylamine hybrid exhibited better antifungal activities than fenfuram.[19]

Inspired by these researches, to extend the researches on the development of novel amide derivatives as fungicides,[19–21] fluxapyroxad was applied as a lead molecule and the diarylamines were introduced in order to replace the substituted biphenyl group in fluxapyroxad based on the principle of "splicing-up" bioactive substructures. A series of novel pyrazole carboxamides with diarylamines scaffold were designed and synthesized (Fig. 2). Subsequently, *in vitro* antifungal activities were performed to evaluate the fungicidal activities against the selected four phytopathogenic fungi *Rhizoctonia solani* (*R. solani*), *Fusarium oxysporum* (*F. oxysporum*), *Phytophthora infestans* (*P. infestans*) and *Fu-*

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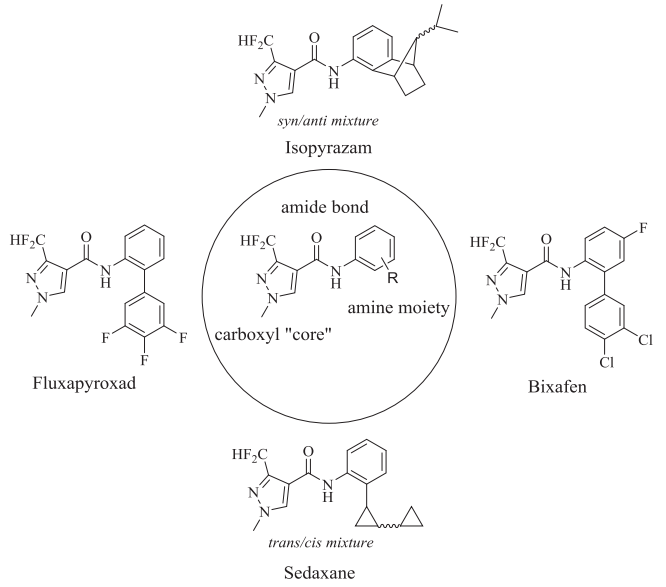


Fig. 1. Representative pyrazole carboxamide fungicides inhibiting succinate dehydrogenase and their prototypical pharmacophore.

sarium graminearum (*F. graminearum*). Furthermore, SDH inhibition

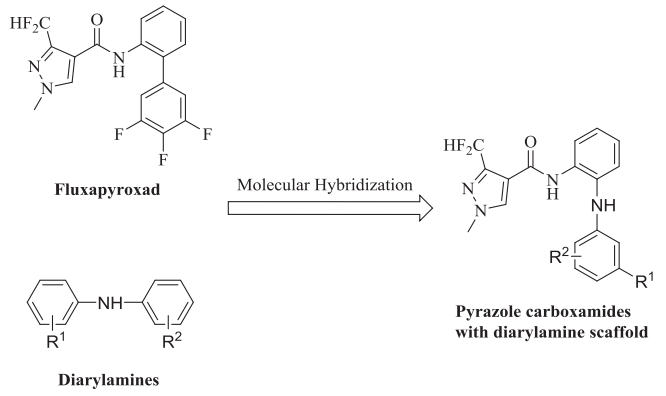
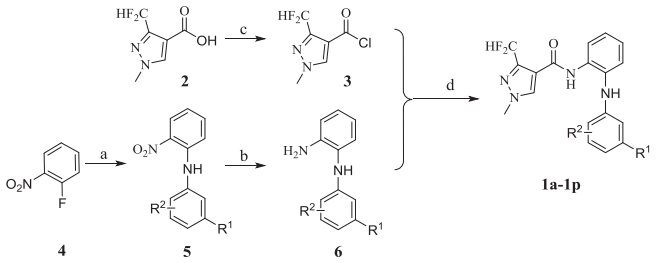


Fig. 2. The strategy for design of novel substituted pyrazole carboxamides with diarylamines scaffold.

activities *in vitro* and molecular docking of target compounds were used in order to verify their potential mechanism.

Scheme 1 and Table 2 detail the syntheses and chemical structures of the target compounds. Initially, compounds **5** were obtained by condensation reaction and transformed into the corresponding compounds **6** through reduction reactions.[13] Meanwhile, the important intermediate compound **3** was prepared via chlorination of the key compound **2** (Scheme 1).[19] Finally, the compound **3** was reacted with the compounds **6** through classical approach to afford a series of novel pyrazole carboxamide fungicides, namely compounds **1a–1p**.[19]

The results of the *in vitro* antifungal activities of the target compounds **1a–1p** and fluxapyroxad at a dosage of 20 mg/L against *R. solani*, *F. oxysporum*, *P. infestans* and *F. graminearum* were listed in Table 1. Here, the antifungal activities were expressed as the inhibition percentage. It was found that the target compounds exhibited fungicidal activities against four fungi. Almost all target compounds showed very



Scheme 1. Synthesis of the target compounds. Reagents and conditions: (a) substituted anilines, KF, 160 °C, 15 h; (b) Fe/NH_4Cl, C_2H_5OH (75%), 2 h; (c) $SOCl_2/CH_2Cl_2$, 80 °C, 3 h; (d) CH_2Cl_2, Et_3N, 0 °C-r.t., 3 h.

strong activities against *R. solani*, however, poor antifungal activities against *F. oxysporum*, *P. infestans* and *F. graminearum* could be observed. For example, except compounds **1a**, **1f**, **1k**, **1m** and **1n**, another eleven compounds displayed much higher fungicidal activities against *R. solani* (over 90% Inhibition rate) and were better than fluxapyroxad.

To analyze the antifungal activities of the target compounds with excellent effects against *R. solani*, the compounds **1a–1p** were selected for further studies. Their EC_{50} values were listed in Table 2. Compounds **1b**, **1c**, **1d**, **1f**, **1g**, **1j**, **1n** and **1p** with EC_{50} values of 0.005–0.028 mg/L showed significant antifungal activities, much more superior to fluxapyroxad (EC_{50} = 0.033 mg/L).

In order to investigate whether the SDH is a potential target enzyme of title compounds or not, the fungal SDH inhibition assay was performed. Compound **1c** and **1j** were selected and tested against SDH *in vitro* from mitochondria of *R. solani*. As demonstrated in Table 3, the selected compound **1c** (IC_{50} = 0.034 mg/L) showed higher inhibition abilities against SDH than fluxapyroxad (IC_{50} = 0.037 mg/L). It further proved that the SDH probably is one of the important action targets of the novel pyrazole carboxamides.

To further survey whether the SDH is a potential target enzyme of novel pyrazole carboxamides with diarylamines scaffold or not, the binding mode of compound **1c** and Fluxapyroxad to SDH was shown in Figs. 3 and 4. The compound **1c** fit in the gap composed of subunit B, C and D (Fig. 3) and the phenyl group in the middle of compound **1c** stretched into the hydrophobic pocket that consisted of the residues B/Pro-202, B/Ile-251, C/Ile-77 and C/Trp-73, while the 2-methylpyrazole scaffold of compound **1c** located at another hydrophobic pocket, surrounded by the residues B/Trp-205, B/Trp-206, C/Phe-64 and C/Trp-73, forming a stable hydrophobic binding. Detailed analysis showed that a π-π stacking interaction was observed between the phenyl group of compound **1c** and sidechain of residue C/Trp-73. The fluxapyroxad also fit in the gap composed of subunit B, C and D and shared a similar binding mode with compound **1c** (Fig. 4). The docking results revealed that the compound **1c** might be potential SDHI.

In summary, a series of novel substituted pyrazole carboxamides were designed and synthesized. Preliminary bioassays showed that some of the target compounds exhibited good antifungal activities against *Rhizoctonia solani*, *Fusarium oxysporum*, *Phytophthora infestans* and *Fusarium graminearum*. Among them, compound **1c** exhibited the highest antifungal activity against *R. solani in vitro* with EC_{50} value of 0.005 mg/L, superior to the lead compound fluxapyroxad (EC_{50} = 0.033 mg/L). And compound **1c** (IC_{50} = 0.034 mg/L) showed higher inhibition ability against SDH than compound fluxapyroxad (IC_{50} = 0.037 mg/L) and it may be a promising lead compound for the potential development of fungicide.

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