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Synthesis of heterocycle-attached methylidenebenzenesulfonohydrazones as antifungal agents

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ABSTRACT

A series of heterocycle-attached methylidenebenzenesulfonohydrazone derivatives were synthesized and evaluated for their antifungal activities against seven phytopathogenic fungi such as *Fusarium graminearum*, *Alternaria solani*, *Valsa mali*, *Phytophthora capsici*, *Fusarium solani*, *Botrytis cinerea*, and *Glomerella cingulata*. Compounds **7b**, **8d**, **9a**, **9b** and **9d** exhibited a good and broad-spectrum of antifungal activities against at least five phytopathogenic fungi at the concentration of 100 μg/mL. It demonstrated that addition of one double bond between the phenylsulfonylhydrazone fragment and the furan ring of **6a**,**b**,**d** could afford more active compounds **9a**,**b**,**d**; however, introduction of the nitro group on the phenyl ring of **6a**–**9a** gave less potent compounds **6e**–**9e**.

The hydrazone skeleton occurs in many biologically active compounds, which display a variety of interesting activities such as anti-inflammatory activity,[1] anticancer activity,[2,3] antibacterial activity,[4,5] cytotoxic activity,[6] antioxidant activity,[7] and antischistosomal activity.[8] More recently, we have found that introduction of phenylsulfonylhydrazone fragments into podophyllotoxin or piperine could result in more potent compounds, that is, podophyllotoxin-based phenylsulfonylhydrazones (**I**, Fig. 1),[9] and piperine-based phenylsulfonylhydrazones (**II**, Fig. 1).[10]

Additionally, some phytopathogenic fungi (e.g., *Fusarium graminearum*, *Alternaria solani*, *Valsa mali*, *Phytophthora capsici*, *Fusarium solani*, *Botrytis cinerea*, and *Glomerella cingulata*) could easily and quickly infect many crops and cause significant yield reductions.[11] Especially some *Fusarium* species also produce terrible mycotoxins such as fumonisins, trichothecenes and zearalenone in cereal crops that are hazardous for human and animal health if they enter the food chain.[12] Obviously, development of bioactive compounds to efficiently control these agricultural fungi is still highly desirable. Consequently, in continuation of our program aimed at the discovery and development of novel antifungal agents, in this Letter we synthesized a series of heterocycle-attached methylidenebenzenesulfonohydrazone derivatives (**III**, Fig. 1). Their antifungal activities were tested against seven phytopathogenic fungi, such as *F. graminearum*, *A. solani*, *V. mali*, *P. capsici*, *F. solani*, *B. cinerea*, and *G. cingulata*.

As shown in Scheme 1, a series of heterocycle-attached methylidenebenzenesulfonohydrazone derivatives (**6a**–**e**, **7a**–**e**, **8a**–**e** and **9a**–**e**) were smoothly obtained by reaction of four heterocyclic aldehydes (**1**–**4**) with different phenylsulfonyl hydrazides (**5a**–**e**) in 51–99% yields. All compounds were well characterized by ^{1}H NMR, HRMS and mp (see the Supplementary data).[13] To obtain the precise three-dimensional structural information, the steric structure of compound **6d** was well determined by single-crystal X-ray diffraction (Fig. 2).[14]

As described in Table 1, first, a series of compounds **6a**–**e**, **7a**–**e**, **8a**–**e** and **9a**–**e** were screened in vitro for their antifungal activities at 100 μg/mL against seven phytopathogenic fungi (e.g., *F. graminearum*, *A. solani*, *V. mali*, *P. capsici*, *F. solani*, *B. cinerea*, and *G. cingulata*).[15] Hymexazol, a commercial agricultural fungicide, was used as a positive control. Among all derivatives, compounds **6d**, **7a**,**b**, **8a**,**b**,**d**, and **9a**,**b**,**d** showed good antifungal activity against *V. mali* with the inhibition rates greater than 50%; compounds **7b**, **8a**,**b**, **d**, and **9d** displayed good antifungal activity against *A. solani*; compounds **6b**,**c**,**d**, and **9a**,**b**,**d** showed good antifungal activity against *F. graminearum*; compound **9a** exhibited good antifungal activity against *P. capsici*; compounds **7b**, **8a**,**b**,**d**, and **9a**,**b**,**d** showed good antifungal activity against *F. solani*; compounds **6b**,**c**,**d**, **7b**, **8d** and **9a**,**b**,**d** exhibited good antifungal activity against *G. cingulata*; compounds **7b** and **8d** displayed good antifungal activity against *B. cinerea*. Two pictures of some compounds inhibiting the growth

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Table 1
Antifungal activities of compounds **6a–e**, **7a–e**, **8a–e** and **9a–e** against seven phytopathogenic fungi at 100 μg/mL[a]

Compd	Antifungal activities (inhibition %)						
	V. mali	*A. solani*	*F. graminearum*	*P. capsici*	*F. solani*	*G. cingulata*	*B. cinerea*
6a	18.3 (±0.3)	4.4 (±0.8)	36.9 (±0.6)	12.6 (±1.9)	0 (±0.8)	26.5 (±0)	7.3 (±0.2)
6b	41.4 (±1.9)	16.6 (±0.8)	59.5 (±3.3)	28.5 (±0.4)	19.2 (±1.0)	63.5 (±0.2)	33.8 (±0.6)
6c	33.9 (±0.6)	25.3 (±2.5)	56.0 (±1.8)	35.2 (±0.7)	16.8 (±0.2)	64.5 (±0.2)	45.7 (±0.2)
6d	52.2 (±0.7)	17.4 (±1.5)	55.4 (±0.9)	32.3 (±1.0)	36.8 (±2.0)	86.5 (±0)	50.6 (±0)
6e	4.1 (±0.3)	8.2 (±0.6)	3.0 (±1.0)	7.3 (±1.5)	0 (±0.6)	17.1 (±0.8)	8.5 (±0.3)
7a	51.9 (±0.3)	17.4 (±0.5)	23.8 (±0.3)	37.6 (±0.7)	43.7 (±1.2)	42.0 (±0.9)	43.6 (±0.2)
7b	62.5 (±0.7)	46.0 (±4.5)	12.5 (±6.3)	46.5 (±0.4)	53.0 (±1.4)	63.3 (±0.6)	60.1 (±0.9)
7c	27.0 (±0.9)	22.3 (±1.3)	6.7 (±1.7)	36.3 (±0.5)	15.9 (±0.8)	42.9 (±0.6)	34.8 (±0.3)
7d	28.4 (±1.5)	16.1 (±0.6)	3.8 (±0.4)	29.6 (±1.8)	27.5 (±1.9)	34.3 (±1.2)	28.7 (±2.0)
7e	22.7 (±0.3)	8.2 (±0.6)	1.4 (±0.3)	24.5 (±1.5)	15.9 (±0.8)	40.8 (±0.4)	36.3 (±0.6)
8a	54.9 (±1.1)	53.4 (±0.8)	24.4 (±1.8)	44.6 (±0.6)	65.7 (±0.4)	42.9 (±0.3)	48.2 (±0.6)
8b	68.4 (±2.1)	58.9 (±1.0)	41.1 (±1.8)	46.8 (±2.0)	73.7 (±0.2)	40.4 (±0.3)	50.3 (±0.4)
8c	49.4 (±1.4)	27.5 (±2.5)	8.5 (±0.6)	40.1 (±0.8)	38.3 (±0.2)	19.2 (±0.3)	25.9 (±0.3)
8d	68.6 (±0.4)	64.6 (±1.4)	30.6 (±1.4)	48.1 (±0.4)	74.6 (±0.7)	53.5 (±0.8)	61.6 (±0.3)
8e	8.0 (±0.8)	9.0 (±0.9)	3.8 (±0.4)	23.4 (±0)	10.8 (±1.7)	3.3 (±0)	5.8 (±0.5)
9a	76.0 (±1.3)	15.8 (±0.6)	86.1 (±5.5)	62.4 (±1.3)	76.0 (±0.4)	54.7 (±0.3)	23.8 (±0.7)
9b	63.4 (±2.7)	28.3 (±2.2)	68.8 (±0.4)	50.3 (±1.7)	69.2 (±0.4)	66.9 (±0.2)	37.5 (±0.4)
9c	41.6 (±0.3)	16.6 (±0.5)	45.2 (±0)	37.4 (±0.4)	39.8 (±0.3)	40.8 (±0.4)	18.0 (±0.3)
9d	83.3 (±0.9)	41.7 (±4.8)	71.8 (±0.2)	45.2 (±1.0)	58.1 (±1.5)	63.0 (±0.2)	56.4 (±1.2)
9e	5.7 (±0.4)	4.9 (±1.4)	2.0 (±1.0)	13.2 (±0.6)	0 (±0.4)	21.2 (±0.4)	19.5 (±0)
Hym[b]	37.8 (±1.3)	27.8 (±1.5)	48.8 (±1.8)	71.0 (±0.3)	43.7 (±0.2)	22.4 (±0.3)	76.2 (±2.5)

[a] Values are means ± S.D. of three replicate.
[b] Hymexazol was used as a positive control.

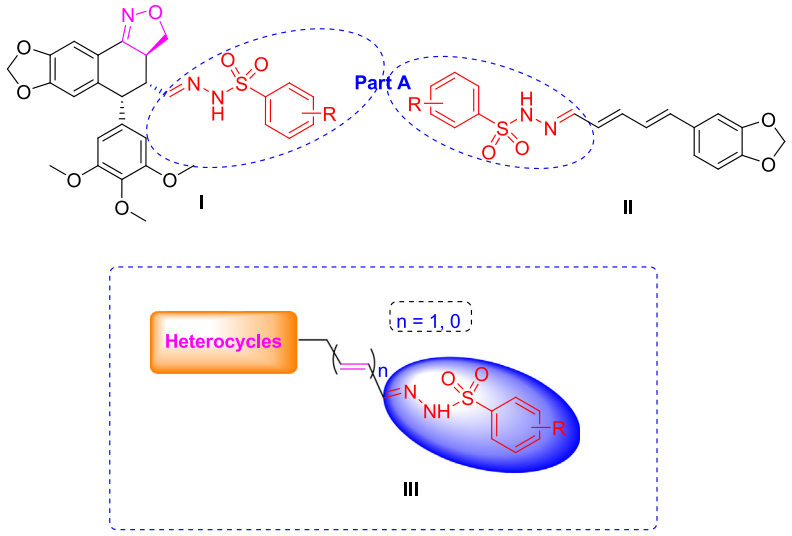

Figure 1. Chemical structures of podophyllotoxin-based phenylsulfonylhydrazones (**I**), piperine-based phenylsulfonylhydrazones (**II**), and the target compounds **III**.

of *F. solani* and *V. mali* were depicted in Figures 3 and 4, respectively. Generally, compounds **7b**, **8d**, **9a**, **9b** and **9d** exhibited a good and broad-spectrum of antifungal activities against at least five phytopathogenic fungi at the concentration of 100 μg/mL. Interestingly, introduction of the ethyl group on the phenyl ring of **7a–9a** afforded more potent compounds than those containing the methyl group on the phenyl ring (e.g., **7e–9e**). However, introduction of the nitro group on the phenyl ring of **6a–9a** afforded the less potent compounds **6e–9e**. On the other hand, addition of one double bond between the phenylsulfonylhydrazone fragment and the furan ring of **6a**,**b**,**d** could usually give more active compounds **9a**,**b**,**d** against six phytopathogenic fungi such as *F. graminearum*, *A. solani*, *V. mali*, *P. capsici*, *F. solani*, and *B. cinerea*.

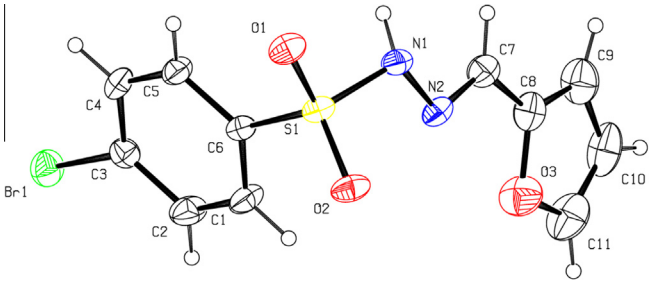

Figure 2. The X-ray crystal structure of compound **6d**.

Subsequently, as shown in Table 2, the EC_{50} values of compounds **6d**, **8b**, **8d**, **9a**, **9b** and **9d** against some phytopathogenic fungi were further calculated. Among them, the EC_{50} values of **8b**, **8d**, and **9a** against *F. solani* were 0.0979, 0.0702, and 0.142 μmol/mL, respectively; whereas the EC_{50} value of hymexazol against *F. solani* was 1.152 μmol/mL. The EC_{50} values of **8b**, **8d**, **9a**, **9b** and **9d** against *V. mali* were 0.113, 0.0838, 0.0904, 0.0833 and