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Discovery of benzotriazole-azo-phenol/aniline derivatives as antifungal agents

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ABSTRACT

A series of benzotriazole-azo-phenol/aniline derivatives were prepared and evaluated for their antifungal activities against six phytopathogenic fungi such as *Fusarium graminearum*, *Fusarium solani*, *Alternaria alternate*, *Valsa mali*, *Botrytis cinerea*, and *Curvularia lunata*. Among them, compounds **IIf**, **IIn**, and **IIr** showed a broad-spectrum of potent antifungal activities. Especially some compounds displayed 3.5–10.8 folds more potent activities than carbendazim against *A. alternata* and *C. lunata*. Notably, compounds **IIc**, **IIm**, and **IIr** exhibited good protective and therapeutic effects against *B. cinerea* at 200 μg/mL. Their structure-activity relationships were also discussed.

Fungicides play a key role in the integrated management of diseases in crops, however, the appearance of resistance in the target pathogens has resulted in limiting the efficacy and useful lifetime of fungicides.[1] Therefore, development of new alternatives for effective control of those agricultural diseases is highly desirable.[2]

Many compounds containing the benzotriazole nucleus (Fig. 1) display a variety of biological properties including CK2 inhibitory activity,[3] antifungal activity,[4–6] antimicrobial activity,[7–10] antiparasitic activity,[7] antiviral activity,[11] and antitumor activity.[7] Previously, we synthesized a series of benzimidazole-zao-phenol derivatives (**I**, Fig. 1) as antifungal agents, and found that some compounds exhibited the potent antifungal activities against five phytopathogenic fungi such as *Fusarium graminearum*, *Alternaria solani*, *Valsa mali*, *Botrytis cinerea*, and *Curvularia lunata*.[12] In continuation of our program aimed at the discovery and development of pesticidal agents,[13–16] here we prepared a series of benzotriazole-azo-phenol hybrids (**II-A**, Fig. 1) as antifungal agents by incorporating the benzotriazole nucleus with the fragment B of **I**; meanwhile, a series of benzotriazole-azo-aniline derivatives (**II-B**, Fig. 1), where the amino group was substituted for the hydroxy of **II-A**, were also synthesized as antifungal agents. Their antifungal activities were tested against six phytopathogenic fungi, such as *Fusarium graminearum*, *Fusarium solani*, *Alternaria alternate*, *Valsa mali*, *Botrytis cinerea*, and *Curvularia lunata*.

As shown in Scheme 1, firstly, 4-nitro-*o*-phenylenediamine (**1**) reacted with sodium nitrite in the presence of acetic acid to afford 5-nitrobenzotriazole (**2**), which was further reduced by $SnCl_2{\cdot}2H_2O$ to give 5-aminobenzotriazole (**3**). On the other hand, 1-naphthol (**4a**) or 2-naphthol (**4b**) reacted with 1,3-dibromopropane or 1,4-dibromobutane to give **5a–c**. Then compounds **6a–f** were obtained by reaction of **5a–c** with resorcinol or hydroquinone (Scheme 2). Finally, as shown in Scheme 3, compound **3** reacted with concentrated hydrochloric acid and sodium nitrite at 0–5 °C to give the corresponding benzenediazonium chloride (**7**), which further reacted with the different phenols/anilines (**4a**,**b**; **6a–f**; **8a–k** or **9a–e**) at 0–5 °C for 3–6 h to give benzotriazole-azo-phenol/aniline derivatives (**IIa–x**). Their structures were well characterized by ^{1}H NMR, HRMS, IR and mp (see Supplementary data).

As shown in Table 1, their antifungal activities of benzotriazole-azo-phenol/aniline derivatives (**IIa–x**) were tested in vitro at 100 μg/mL against six phytopathogenic fungi such as *Fusarium graminearum*, *Alternaria alternate*, *Fusarium solani*, *Valsa mali*, *Botrytis cinerea*, and *Curvularia lunata*. Carbendazim, a commercial agricultural fungicide, was used as a positive control. Analysis of variance (ANOVA) was followed by Duncan's post test, which was

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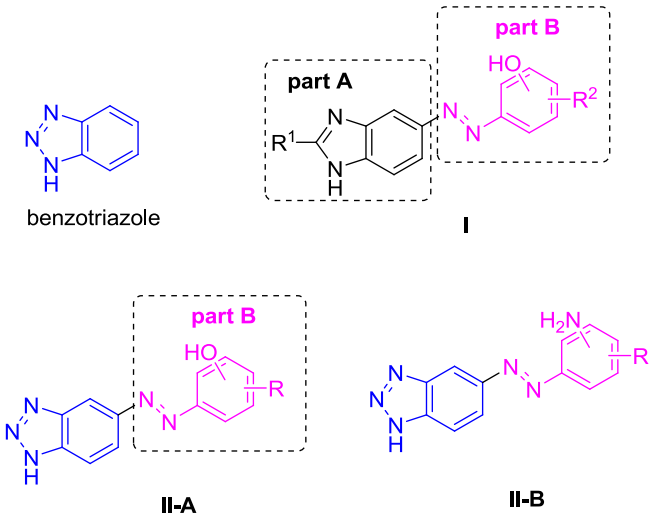
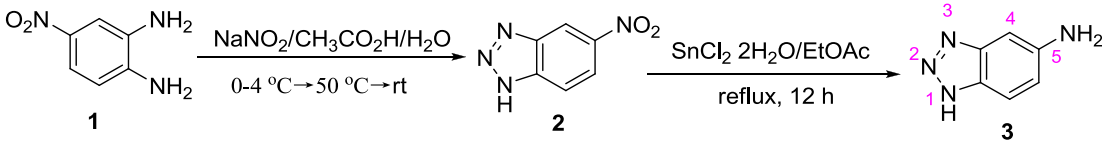


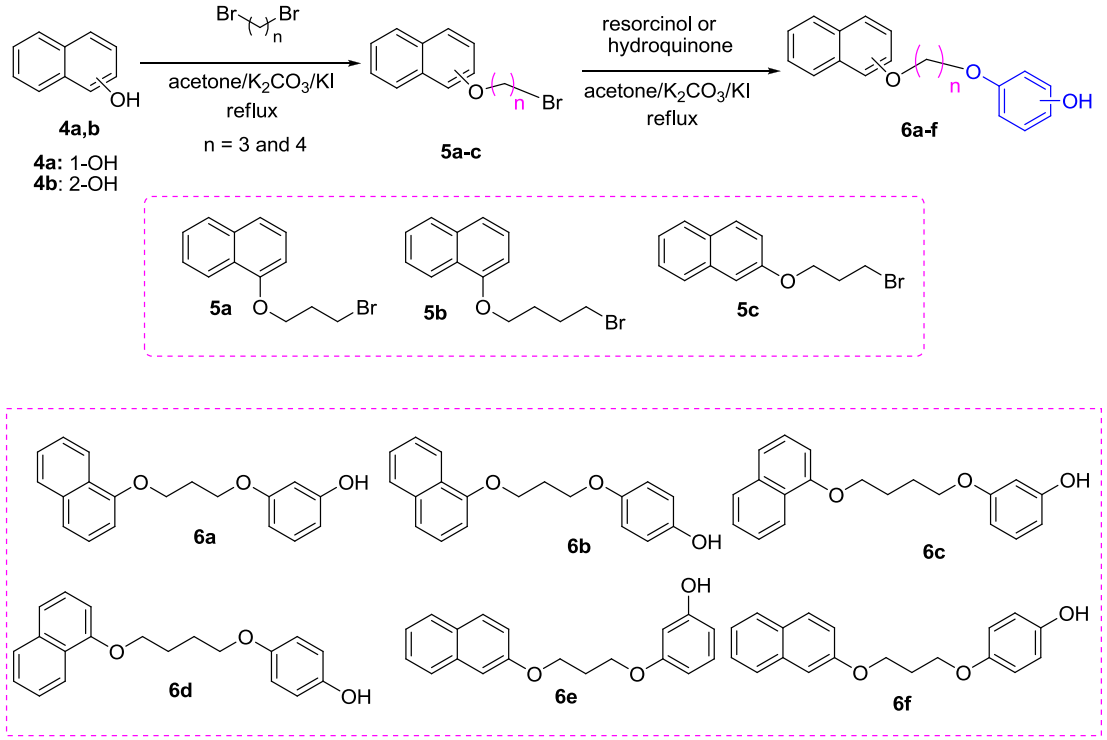
Fig. 1. The chemical structures of benzotriazole, benzimidazole-azo-phenols (**I**), benzotriazole-azo-phenols (**II-A**), and benzotriazole-azo-anilines (**II-B**).

conducted using SPSS 20 for Windows 7. Among all derivatives, compounds **IIa**, **IIf**, **IIh**, **IIn**, **IIp**, **IIr**, and **IIw** showed the good antifungal activity against *V. mali*; compounds **IIf**, **IIn**, **IIo**, and **IIr** showed the good antifungal activity against *C. lunata*; compounds **IIa**, **IIf**, **IIh**, **IIn**, **IIp**, and **IIr** showed the good antifungal activity against *F. solani*; compounds **IIc**, **IId**, **IIf**, **IIh**, **IIk**, **IIn**, **IIo**, **IIr–u**, and **IIw** showed the good antifungal activity against *A. alternata*; compounds **2**, **IIa**, **IIc–f**, **IIh**, **IIi**, **IIk**, **IIm–r**, **IIt**, **IIu**, and **IIw** showed the good antifungal activity against *F. graminearum*; compounds **2**, **IIa**, **IIc**, **IIf**, **IIk**, **IIm–o**, **IIr**, **IIt**, **IIu**, and **IIw** showed the good antifungal activity against *B. cinerea*. Especially compounds **IIf**, **IIn**, and **IIr** showed a broad-spectrum of antifungal activities against six tested phytopathogenic fungi.

To benzotriazole-azo-phenol derivatives (**IIa–j**), compound **IIf** containing the 4-*tert*-butyl and 1-hydroxy groups on the phenyl ring, showed an excellent and a broad-spectrum of antifungal activities against six tested phytopathogenic fungi. The inhibition rates of **IIf** at 100 μg/mL against *V. mali*, *C. lunata*, *F. solani*, *A. alternata*, *F. graminearum*, and *B. cinerea* were 72.8%, 77.6%, 83.4%, 82.1%, 72.1%, and 82.8%, respectively. However, when other groups such as methyl, chlorine atom, methoxy, ethyl, and hydroxy were at the 4-position of the phenyl ring, the antifungal activities of the corresponding compounds were generally not good (Table 1). It demonstrated that the *tert*-butyl group at the 4-position of the phenyl ring was very important for the activities. This result was the same with that of benzimidazole-zao-phenol derivaives.[12] To benzotriazole-azo-aniline derivatives (**IIk–o**), compound **IIn** con-



Scheme 1. Synthesis of 5-aminobenzotriazole (**3**).



Scheme 2. Synthesis of intermediates **6a–f**.