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Short communication

Antifungal agents. Part 4: Synthesis and antifungal activities of novel indole[1,2-*c*]-1,2,4-benzotriazine derivatives against phytopathogenic fungi *in vitro*

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ABSTRACT

A series of novel indole[1,2-*c*]-1,2,4-benzotriazine derivatives were obtained by a modified Sandmeyer reaction in the presence of *tert*-butylnitrite (*t*-BuONO). As compared with hymexazol, a commercially available agricultural fungicide, at the concentration of 50 μg/mL, two indole[1,2-*c*]-1,2,4-benzotriazines, **5h** and **5k**, exhibited the more promising and pronounced antifungal activities *in vitro* against five phytopathogenic fungi. It clearly demonstrated that introduction of appropriate substituents on the indolyl ring of indole[1,2-*c*]-1,2,4-benzotriazine (**5a**) would lead to the more potent derivatives.

1. Introduction

Phytopathogenic fungi, which are hard to control, easily infect many crops, therefore development of new compounds that effectively inhibit those agricultural diseases is still highly desirable. The indole moiety (**I**, Fig. 1) represents an important structural component associated with a variety of alkaloids [1,2] and wide-ranging biological activities, such as antiviral activities [3–7], antitumor activities [8,9], antimicrobial activities [10,11], antituberculosis activities [12], and antifungal activities [13]. Meanwhile, the benzotriazine derivatives (**II**, Fig. 1) have also gained widespread interest due to their broad potential activities [14]. Recently, fragment-based lead discovery has emerged as a more rational and focused approach for molecular modification and drug design. As a part of our ongoing program aimed at the discovery and development of compounds with superior bioactivities [15–18], consequently, in this article we designed and prepared some novel indole[1,2-*c*]-1,2,4-benzotriazine derivatives (**5a**–**k**, Fig. 1) by combinatorial optimization of the indole unit with the benzotriazine moiety, and wanted to investigate their antifungal activities against phytopathogenic fungi.

2. Results and discussion

2.1. Chemistry

As shown in Scheme 1, 5-bromoindole (**1b**) was prepared from indole (**1a**) in the presence of ethanol and 27% aqueous sodium bisulfite, followed by reaction with acetic anhydride and bromine [19]. Then **1b** reacted with sodium methoxide in the presence of cuprous iodide (CuI) and *N*,*N*-dimethylformamide (DMF) to give 5-methoxyindole (**1c**). As outlined in Scheme 2, indole derivatives (**1a**–**h**) firstly reacted with 2-nitrophenyl halides (**2a** and **b**) by the S_NAr reaction mediated with cesium carbonate (Cs_2CO_3) to yield **3a**–**j** [20], which were subsequently reduced to **4a**–**j** in the presence of stannous chloride dihydrate ($SnCl_2{\cdot}2H_2O$). Finally, indole [1,2-*c*]-1,2,4-benzotriazine derivatives (**5a**–**j**) were obtained from **4a**–**j** by a modified Sandmeyer reaction *via* the intramolecular cyclization in the presence of *tert*-butylnitrite (*t*-BuONO). Compound **5k** was synthesized starting from indole as described in Scheme 3. At first, **1a** reacted with DMF in the presence of phosphorus chloride oxide ($POCl_3$) to produce 3-formylindole (**1i**) [21], which further reacted with 2-fluoronitrobenzene by the S_NAr

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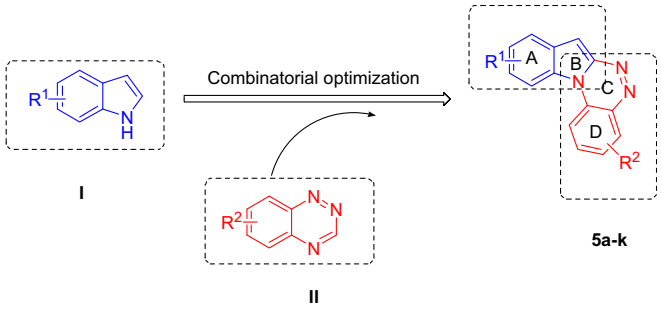


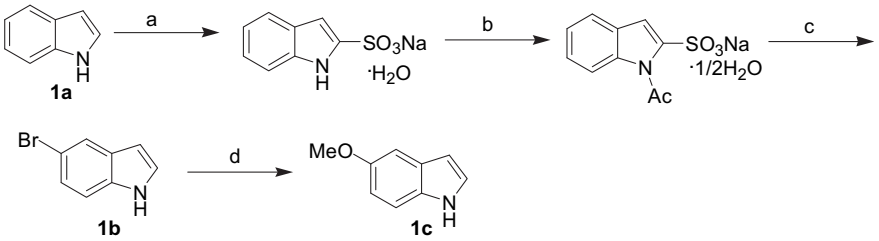
Fig. 1. Design strategy of the target compounds **5a**–**k**.

reaction to give **3k**. Then **3k** was reduced to **4k** by $SnCl_2 \cdot 2H_2O$, and **4k** was further reduced to **4l** with sodium borohydride ($NaBH_4$). At last, **4l** reacted with *t*-BuONO to give **5k** *via* the intramolecular cyclization. However, the diazonium salt of **4k** did not cyclize to produce **5l** at all. The structures of the target compounds were well characterized by ^1H NMR, ^{13}C NMR, m.p., HRMS or MS.

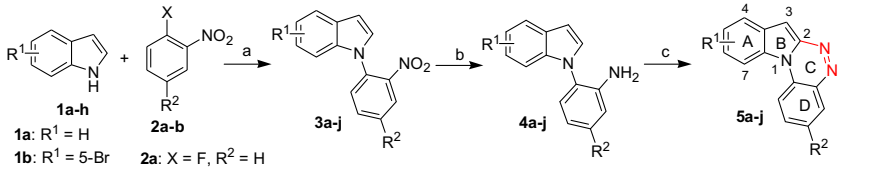
2.2. Antifungal activity

The antifungal activities of 11 novel indole[1,2-*c*]-1,2,4-benzotriazine derivatives (**5a**–**k**) against five phytopathogenic fungi (*i.e.*, *Fusarium graminearum*, *Alternaria alternata*, *Pyricularia oryzae*, *Fusarium oxysporum* f. sp. *vasinfectum*, and *Alternaria brassicae*) were investigated at the concentration of 50 μg/mL *in vitro* by poisoned food technique [22]. Hymexazol, a commercially available agricultural fungicide, was used as a positive control at 50 μg/mL.

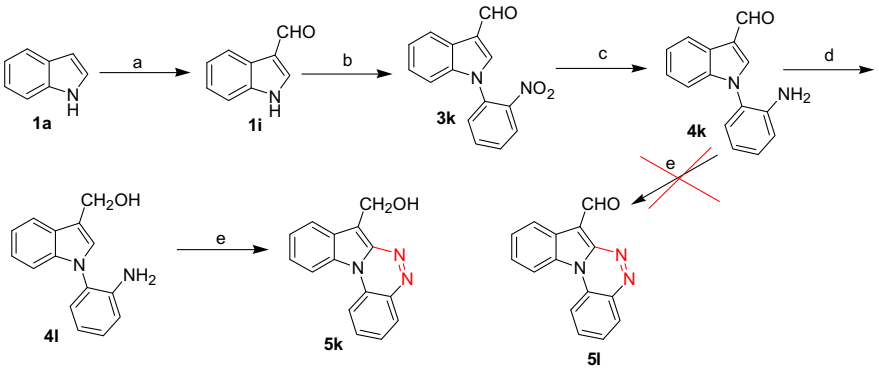
As outlined in Table 1, among all the derivatives, compounds **5h** and **5k** generally exhibited the more promising and pronounced antifungal activities than hymexazol. Through a comparative study on the relationship between the chemical structures and antifungal activities of **5a**–**k** (SAR), some interesting results were described as follows: (1) In general, introduction of the phenylaminocarbonyl substituent on the D-ring of **5a** or **5d** gave **5i** or **5j**, the corresponding antifungal activities of which were decreased as compared with **5a** and **5d**, respectively. For example, the inhibition



Scheme 1. Synthesis of compounds **1b** and **1c**. *Reagents and conditions*: (a) 27% aq. $NaHSO_3$, EtOH, rt, 20 h, 98%; (b) Ac_2O, 70 °C, 2 h, then 90 °C, 0.5 h, 89%; (c) Br_2, H_2O, 0–5 °C, 1 h, then rt, 1 h, 74%; (d) MeONa, DMF, CuI, reflux, 6 h, 98%.



Scheme 2. The synthetic route of compounds **5a**–**j**. *Reagents and conditions*: (a) Cs_2CO_3, DMSO, 40 °C, 2–8 h, 21–99%; (b) $SnCl_2 \cdot 2H_2O$, EtOAc, reflux, 1–4 h, 44–93%; (c) *t*-BuONO, MeCN, rt, 1/6–22 h, 24–99%.



Scheme 3. The synthetic route of compound **5k**. *Reagents and conditions*: (a) $POCl_3$, DMF, 0 °C, 20 min, then 40 °C, 1 h, then 20% aq. NaOH, 0 °C, then reflux, 6 h, 96%; (b) Cs_2CO_3, 2-fluoronitrobenzene, DMSO, 40 °C, 5 h; (c) $SnCl_2 \cdot 2H_2O$, EtOAc, reflux, 22 h, 29% (from **1i** to **4k**); (d) $NaBH_4$, MeOH, rt, 1 h, 78%; (e) *t*-BuONO, MeCN, rt, 0.5 h, 66%.