European Journal of Medicinal Chemistry 120 (2016) 244–251

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Research paper

Design, synthesis and antifungal activity of novel furancarboxamide derivatives

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ARTICLE INFO

Article history:
Received 22 September 2014
Received in revised form
19 April 2016
Accepted 22 April 2016
Available online 26 April 2016

Keywords:
Furancarboxamides
Synthesis
Antifungal activity
Diphenyl ether

ABSTRACT

Twenty-seven novel furancarboxamide derivatives with a diphenyl ether moiety were synthesized and evaluated for their antifungal activity against *Rhizoctonia solani*, *Botrytis cirerea*, *Valsa mali* and *Sphaceloma ampelimum*. Antifungal bioassay results indicated that most compounds had good or excellent fungicidal activities for *R. solani* and *S. ampelimum* at 20 mg L^{-1}. Among synthesized compounds, compound **18e** showed a greater inhibitory effect against *S. ampelimum*, with half maximal effective concentration (EC_{50}) values of 0.020 mg L^{-1}. This strong activity rivals currently used commercial fungicides, such as Boscalid and Carbendazim, and has great potential as a lead compound for future development of novel fungicides.

1. Introduction

Fungal infections cause a persistent burden on human, animal and plants health worldwide [1–7]. Since the 1970s, chemical control of agricultural fungal diseases was mainly achieved by several classes of chemicals, including carboxamides, methoxyacrylates, pyrimidinamines and triazoles [8–10]. Among them, carboxamide fungicides have played an important role in the fungicide market [11,12], with the ability to inhibit the growth of pathogens and can cause their eventual death by interfering with the pathogen respiration systems [13,14]. One class of the carboxamide fungicides are furancarboxamide fungicides, such as Fenfuram, Furancarbanil and Methfuroxam (Fig. 1) [15]. The furancarboxamide fungicides harbor effective antifungal activities [16–18], however fungicide resistance is beginning to emerge in fungal populations [19,20].

Past research has demonstrated that the diphenyl ether derivatives with biological activities are found in a number of natural products, and they have pharmacologically powerful properties [21,22], such as antifungal, antibiotic, antimitotic and immunosuppressive activities [23–26].

In our previous work, many diphenyl ether derivatives were synthesized and found to have good antibacterial activities [27,28]. Recently, on the basis of the principle of "splicing-up" bioactive substructures we synthesized a class of nicotinamide derivatives containing a diphenyl ether moiety [29]. Bioassays indicated that the nicotinamide derivatives had better antifungal activities than Boscalid. To extend our research work on developing furancarboxamides [30], based on the principle of splicing-up bioactive substructures, we exchanged a phenyl group with a more potent diphenyl ether moiety in the present work (Fig. 2).

A series of novel furancarboxamide derivatives with a diphenyl ether moiety were synthesized and subsequently tested for their antifungal activity against *Rhizoctonia solani*, *Botrytis cirerea*, *Valsa mali* and *Sphaceloma ampelimum*. To the best of our knowledge, this is the first report of furancarboxamide derivatives with a diphenyl ether moiety with potent controlling effects against *R. solani* and *S. ampelimum*.

2. Results and discussion

2.1. Chemistry

The synthesis of intermediates and target compounds was performed as illustrated in Schemes 1–4 and Table 1. To synthesize target compounds **17a-17i**, **18a-18i** and **19a-19i**, two classes of important intermediates were prepared. One class was compound

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http://dx.doi.org/10.1016/j.ejmech.2016.04.060
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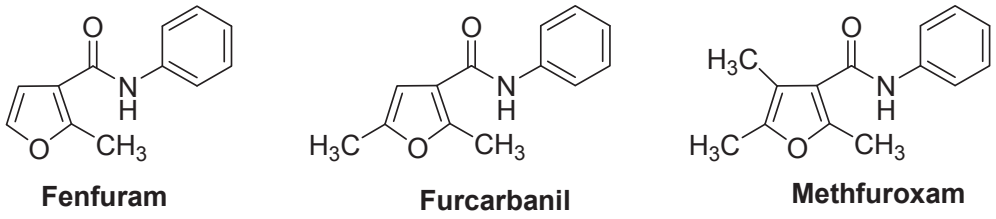


Fig. 1. The commercial furancarboxamide fungicides.

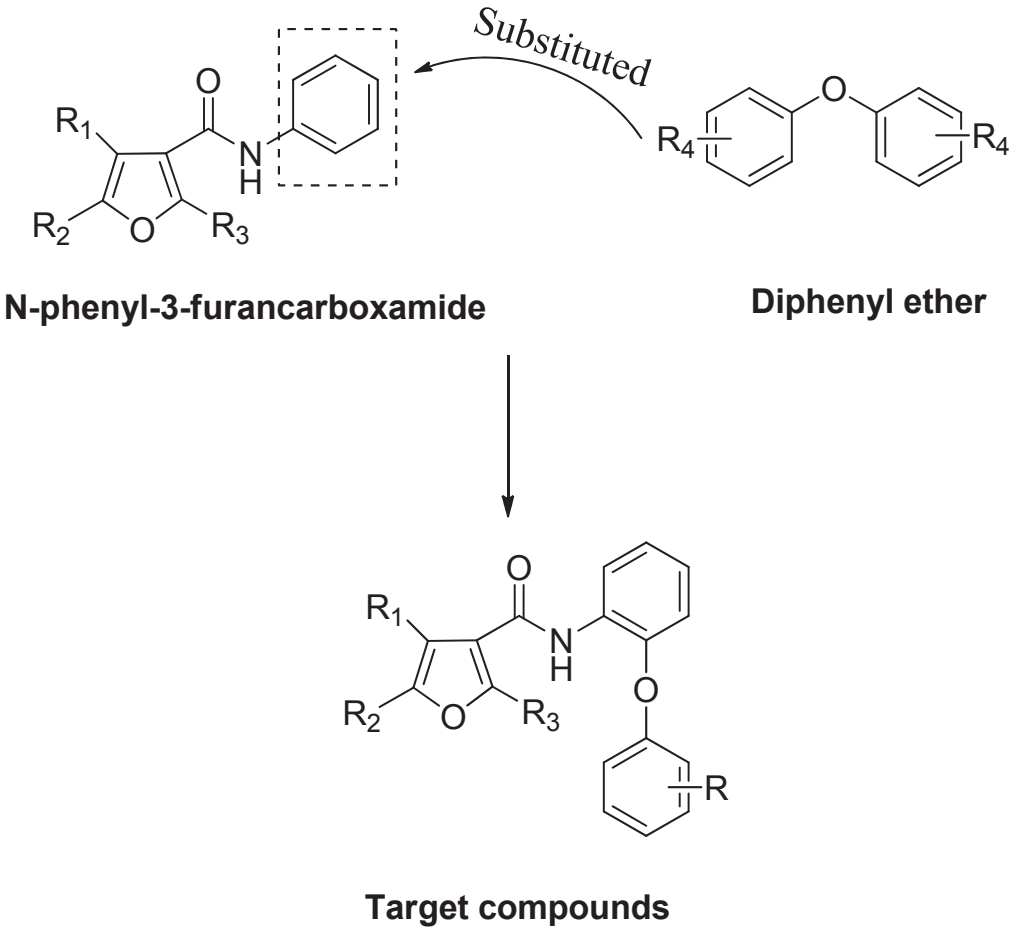
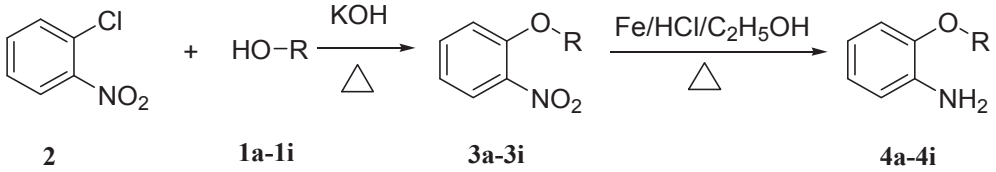


Fig. 2. Design strategy of the target compounds.



a: R= phenyl; **b**: R= 4-fluorophenyl; **c**: R= 4-chlorophenyl; **d**: R= 2-chlorophenyl; **e**: R= 2,4-dichlorophenyl; **f**: R= 2-methylphenyl; **g**: R= 3-methylphenyl; **h**: R= 4-methoxylphenyl; **i**: R= 2-methoxylphenyl.

Scheme 1. Synthesis of 2-amine-aryloxybenzenes (**4a-4i**).

4 and another class was compounds **8** and **13**. Compound **4** was prepared in two steps as previously described [31,32]. First, compound **2** was allowed to react with compound **1** under KOH by condensation reaction to produce compound **3**. Then it was