Chinese Chemical Letters xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Chinese Chemical Letters

journal homepage: www.elsevier.com/locate/cclet

Original article

Synthesis and biological activity of novel N-(3-furan-2-yl-1-phenyl-1H-pyrazol-5-yl) amides derivatives

Jing-Qian Huo [a], Liu-Yong Ma [b], Zhe Zhang [a], Zhi-Jin Fan [b,c,*], Jin-Lin Zhang [a,*], Tetyana V. Beryozkina [d], Vasiliy A. Bakulev [d]

[a] College of Plant Protection, Agricultural University of Hebei, Baoding 071001, China
[b] State Key Laboratory of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China
[c] Collaborative Innovation Center of Chemical Science and Engineering (Tianjin), Nankai University, Tianjin 300071, China
[d] The Ural Federal University Named after the First President of Russia B.N. Yeltsin, Ekaterinburg 620002, Russia

ARTICLE INFO

Article history:
Received 23 May 2016
Received in revised form 2 June 2016
Accepted 7 June 2016
Available online xxx

Keywords:
Amides derivative
Pyrazole
Furan
Synthesis
Herbicidal activity
Fungicidal activity

ABSTRACT

A series of novel *N*-(3-furan-2-yl-1-phenyl-1*H*-pyrazol-5-yl) amides derivatives were designed and synthesized. Their structures were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. All title compounds were evaluated for their herbicidal and antifungal activities. Preliminary bioassay results indicated that the title compounds showed good to moderate herbicidal activity at 1000 mg/L. Compound **6q** presented the best activity against *Digitaria sanguinalis* (L) Scop., *Amaranthus retroflexus* L. and *Arabidopsis thaliana* with an inhibition degree of five. Compound **6d** also showed an inhibition degree of five against *D. sanguinalis*. In addition, at 50 mg/L, most compounds exhibited good *in vitro* antifungal activity against *Sclerotinia sclerotiorum*, with compound **6c** showing over 90% antifungal activity against *S. sclerotiorum* and *Pellicularia sasakii*.

1. Introduction

Pesticides play an important role in agricultural development in our country. However, pesticide resistance has become a serious concern due to continuous application of a single pesticide with a unique mode of action [1–5], Natural products, often having new modes of action, low-residue and high selectivity, are important pesticide leads [6], and following structure optimization, natural products are strong candidates for the pesticide market [7,8]. Identifying new lead compounds is imperative for pesticide development [9,10]. In recent years, the combination of computer simulation, chemical synthesis and biological testing has become the new policy for drug development in the post genomic era [11]. This has an important impact on novel pesticide development.

Transketolase is widely distributed among plants, animals, fungi and bacteria [12], and plays an important role in the calvin cycle of plant photosynthesis [13,14]. It has potential as a new herbicide target [15]. In a previous study, using computer-aided drug screening technology, an amide compound 12007063, with good biological activity, which targeted transketolase was discovered. Amide compounds are widely used as pesticides. For example, propanil belongs to the photosystem PSII herbicides, and fluopyram which belongs to SDHI (succinate dehydrogenase inhibitors) fungicides is also an amide compound. In this study, a series of *N*-(3-furan-2-yl-1-phenyl-1*H*-pyrazol-5-yl) amide derivatives were designed and synthesized for biological screening from lead compound 12007063 by introducing bioactive substructures into the target molecules using the principle of pesticide molecular designation (Fig. 1).

2. Experimental

2.1. Chemistry

Reagents and solvents were analytical grade and the anhydrous reagents were dried by standard methods. The melting points were measured on an XT-4A apparatus and uncorrected. NMR spectra were obtained on a Bruker AV-400 spectrometer operating at 400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR. NMR resonances were registered using $CDCl_3$ as solvents and TMS as the internal

* Corresponding authors.
E-mail addresses: fanzj@nankai.edu.cn (Z.-J. Fan), zhangjinlin@hebau.edu.cn (J.-L. Zhang).

http://dx.doi.org/10.1016/j.cclet.2016.06.019

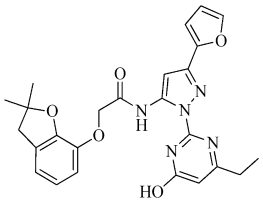


Fig. 1. The structure of herbicide lead compound 12007063.

standard. The high resolution mass spectra were recorded on an Agilent 6520-QTOF LC/MS having ESI source in positive mode.

Synthesis of the title compounds was conducted as shown in Scheme 1. Methyl furan-2-carboxylate (compound **1**) was prepared according to literature [16]. Intermediate **2** was prepared *via* the reaction of methyl furan-2-carboxylate with CH_3CN and NaH in toluene by refluxing for 24 h [17]. The cyclization of compound **2** with phenylhydrazine gave intermediate **3**. Compounds **5a–5t** were obtained by the reaction of **4a–4t** with $SOCl_2$ and a catalytic amount of DMF by refluxing. Compounds **6a–6t** were synthesized by way of a condensation reaction using Et_3N as the base in CH_2Cl_2. The structures of all newly synthesized compounds were characterized by melting points, ^1H NMR, ^{13}C NMR and HRMS.

2.2. Biological assay

The herbicide activity of the target compounds was evaluated through foliar treatment [18]. The symptoms were monitored at 48 h post-treatment and compared with the control group. The grading standard [19] for the inhibition effect is shown in Table 1. The target plants tested for herbicide efficacy were *Digitaria sanguinalis* L., *Echinochloa crusgalli* L., *Amaranthus retroflexus* L., *Portulaca oleracea* L. and *Arabidopsis thaliana*.

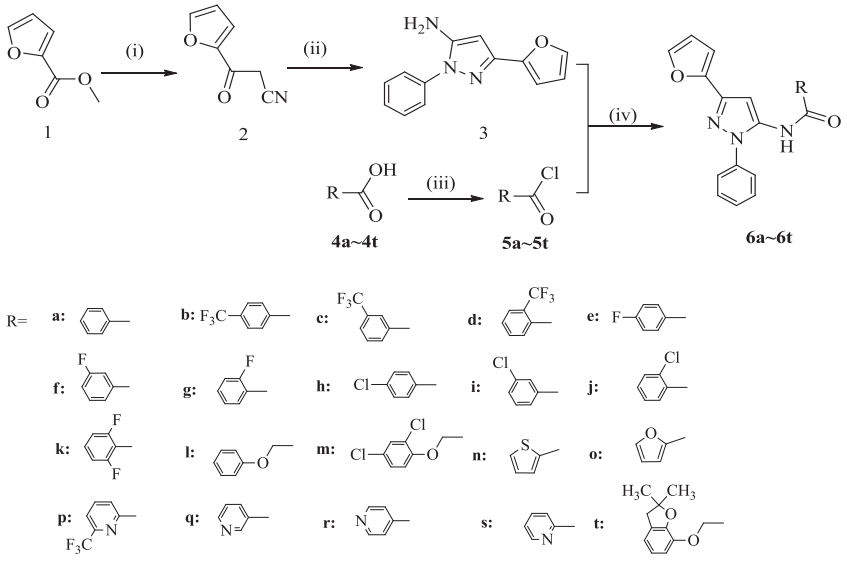
The fungicide activity of the target compounds was tested using the fungi growth inhibition method [20]. Representative fungi used in this study included *Alternaria solani* (AS), *Botrytis cinerea* (BC), *Cercospora arachidicola*(CA), *Gibberella zeae* (GZ), *Phytophthora infestans* (Mont) *de Bary* (PI), *Physalospora piricola* (PP), *Pellicularia sasakii* (PS), *Sclerotinia sclerotiorum* (SS), and *Rhizoctonia cerealis* (RC).

3. Results and discussion

3.1. Synthesis

Heterocyclic compounds are important lead sources for drug and pesticide development and the methods for their construction are well reported [21–23]. Our former research discovered one compound, containing furan and pyrazole ring, which could be studied as an herbicide lead. This study focused on optimization of this lead and a series of novel *N*-(3-furan-2-yl-1-phenyl-1*H*-pyrazol-5-yl) amides derivatives from 3-(furan-2-yl)-1 -phenyl-*H*-pyrazol-5-amine **(3)** was synthesized. We first tried to prepare 3-(furan-2-yl)-1-phenyl-*H*-pyrazol-5-amine **(3)** using EtOH as the solvent, and the cycling reaction of 2-furoylacetonitrile with phenylhydrazine was progressed at the reflux temperature. By-product was formed and the yield of the desired product was low. However, after optimization of the reaction conditions, the yield was increased from 54.01% to 90.09% [24]. 2-Furoylacetonitrile was allowed to react with phenylhydrazine at 130 °C for 1 h, and the desired 3-(furan-2-yl)-1-phenyl-*H*-pyrazol-5-amine **(3)** was successfully generated with over 90% yield.

During the synthesis of the target compounds **(6)**, intermediate **3** did not react completely, and the retention factor values of the target compounds and intermediate **3** were very close. It was difficult to separate and purify the target compounds using column chromatography. After washing with HCl, the alkalic intermediate was easily moved, and the purification efficiency of the target compounds by chromatography was significantly improved. The chemical structures of the target compounds were confirmed by spectroscopic data, and these data are given in Supporting information. Here, the spectroscopic data of **6t** were given as a representative. **6t**: ^1H NMR (400 MHz, $CDCl_3$): δ 8.82 (s, 1H, NH), 7.49 (d, 3H, J = 7.2 Hz, Ph-H), 7.43 (dd, 3H, J = 15.7, 7.6 Hz, Ar-H), 7.09 (s, 1H, Pyrazole-H), 6.90 (d, 1H, J = 7.3 Hz, Ph-H), 6.79 (d, 1H, J = 8.1 Hz, Ph-H), 6.77 (d, 1H, J = 3.5 Hz, Furan -H), 6.67 (d, 1H, J = 8.0 Hz, Ph-H), 6.51 (d, 1H, J = 1.7 Hz, Furan-H), 4.73 (s, 2H, $-OCH_2-$), 3.04 (s, 2H, CH_2), 1.43 (s, 6H, 2× CH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 165.77, 148.34, 147.67, 144.48, 142.22, 141.68, 137.51, 135.56, 129.80, 129.47, 128.38, 124.57, 120.73, 119.90, 114.59, 111.31, 106.75, 95.44, 88.16, 69.20, 43.07, 28.18. HRMS(ESI) $[M+H]^+$ calcd. for $C_{25}H_{23}N_3O_4$: 430.1767, found: 430.1760.



(i) CH_3CN (3.0 equiv.), NaH (3.0 equiv.), Toluene, reflux for 24 h; (ii) Phenylhydrazine (1.0 equiv.), 130 °C for 1 h, yield 90.09%; (iii) $SOCl_2$ (5.0 equiv.), DMF (a catalytic amount), reflux for 5 h; (iv) Et_3N (1.2 equiv.), CH_2Cl, room temperature overnight.

Scheme 1. Synthesis of the target compounds.

Please cite this article in press as: J.-Q. Huo, et al., Synthesis and biological activity of novel N-(3-furan-2-yl-1-phenyl-1H-pyrazol-5-yl) amides derivatives, Chin. Chem. Lett. (2016), http://dx.doi.org/10.1016/j.cclet.2016.06.019