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Original article

Synthesis and biological activities of some fluorine- and piperazine-containing 1,2,4-triazole thione derivatives

Li-Yuan Zhang, Bao-Lei Wang *, Yi-Zhou Zhan, Yan Zhang, Xiao Zhang, Zheng-Ming Li *

State Key Laboratory of Elemento-Organic Chemistry, Collaborative Innovation Center of Chemical Science and Engineering, Nankai University, Tianjin 300071, China

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ABSTRACT

A series of fluorine- and piperazine-containing 1,2,4-triazole thione derivatives were synthesized by the Mannich reaction of triazole intermediates with various substituted piperazines and formaldehyde in high yields. Structures of title compounds were confirmed by melting points, IR, ^{1}H NMR, ^{13}C NMR and elemental analysis. The preliminary bioassays for 17 novel title compounds showed that several compounds have significant fungicidal activity against *Cercospora arachidicola*, *Physalospora piricola* and *Rhizoctonia cerealis* at 50 μg/mL.

1. Introduction

Due to the excellent selectivity, low toxicity and versatile biological activities, the chemistry of nitrogen containing heterocyclic compounds has been a hot topic in pharmaceutical and pesticidal research areas [1]. As one of the five-membered nitrogen-containing heterocycles, 1,2,4-triazole introduced into compounds will contribute to a wide-range spectrum of biological activities including anti-inflammatory [2], anticancer [3,4], antifungal [5], insecticidal [6], and plant growth regulating activities [7]. Furthermore, piperazine ring is one of the important heterocycles and has various properties such as low toxicity, easy forming multiple hydrogen bonds or ionic bonds, and functional effect that modulating drug lipid water partition coefficient and acid-base equilibrium constant. Therefore it is often introduced into some parent structures to enhance the biological properties during the drug design. It has been found that *N*-substituted piperazine compounds have a wide range of biological activities, such as antimicrobial [8], anticancer [9], herbicidal and insecticidal activities [10], especially they were often used as antimicrobial agent. Mannich bases of 1,2,4-triazole derivatives containing *N*-substituted piperazine moiety have been reported to possess antifungal activity [11,12], and some piperazine-containing 4,5-disubstituted-1,2,4-triazole Mannich bases were found to have tuberculostatic activity [13]. However, there are comparatively few literatures about the piperazine-containing compounds for the design and development of agrochemicals.

In our early work, some 1,2,4-triazole Mannich bases containing piperazine and trifluoromethyl groups were synthesized through Mannich reaction, and found to possess significant fungicidal and herbicidal activities [14,15], which encourage us to carry out further study on this topic. Therefore a series of novel fluorine- and piperazine-containing 1,2,4-triazole thione derivatives were herein designed and synthesized. According to the structure of the lead compound, 1-(4-substitutedpyrimidylpiperazin-1-yl)methyl-4-(substituted)benzylideneamino-3-trifluoromethyl-1,2,4-triazole-5-thione [14] we reported previously and in view of the importance of fluorine in enhancing bioactivities of various compounds, our intentions were to retain the main structural feature of triazole thione and piperazine moieties of lead compound, change trifluoromethyl group on triazole ring to fluorine-containing aryl group or methyl group, (substituted)benzylideneamino group to phenyl or arylamide group, and study the synthesis and the pesticidal activities of new triazole thione Mannich bases with diverse structures. There are many literatures reported the syntheses of triazole Mannich bases [16–18], while there is no literature about such kind of compounds bearing an

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* Corresponding authors.
E-mail addresses: nkwbl@nankai.edu.cn (B.-L. Wang), nkzml@vip.163.com (Z.-M. Li).

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o-fluorophenyl and a phenyl at 3- and 4-position respectively of 1,2,4-triazole ring, and various substituted piperazine moiety (substituted benzyl piperazine, phenyl piperazine, (pyridin-2-yl)piperazine, 4,6-disubstituted pyrimidyl piperazine) as amine part of Mannich base, also the symmetric bis(triazole) Mannich bases containing these structural factors. In particular, the Mannich reaction of 1,2,4-triazole thiol containing arylamide group has not been studied so far. In this paper these novel structures designed were successfully synthesized and their herbicidal and fungicidal activities were evaluated.

2. Experimental

Melting points were determined using an X-4 binocular microscope apparatus and uncorrected. Infrared spectra (IR) (potassium bromide) were recorded on a Bruker Tensor 27 spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were measured on a Bruker AV-400 instrument (400 MHz) using TMS as an internal standard. Elemental analyses were performed on an elementar Vario EL CUBE elemental analyzer.

Intermediates 4-(4,6-disubstituted pyrimidin-2-yl) piperazine, 4-(substituted)benzylpiperazines, 4-phenyl-5-(2-fluorophenyl)-4*H*-1,2,4-trizole-3-thiol, 4-Amino-5-methyl-4*H*-1,2,4-trizole-3-thiol were prepared according to the literature [19–22].

2.1. General synthetic procedures for N-(3-mercapto-5-methyl-4H-1,2,4-triazol-4-yl)-2/3-fluorobenzamide (**3**)

The procedures are similar to that described previously [23]. To the *o*-fluorobenzoyl chloride (7.9 g, 0.5 mol) was added a solution of 4-amino-5-methyl-4*H*-1,2,4-triazole-3-thiol (6.5 g, 0.5 mol) in anhydrous acetonitrile (30 mL) under stirring at 80 °C. The mixture was refluxed and stirred for 4 h, the solid precipitated was filtered and washed with acetonitrile to give compound **3**.

3a: White solid, yield 85%, mp 251–252 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.79 (s, 1H, SH), 12.02 (s, 1H, NH), 7.88 (d, 1H, J = 7.7 Hz, Ph-H), 7.81 (dd, 1H, J = 9.5, 1.7 Hz, Ph-H), 7.67 (m, 1H, Ph-H), 7.56 (m, 1H, Ph-H), 2.22 (s, 3H, CH_3).

3b: White solid, yield 86%, mp 255–256 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 13.73 (s, 1H, SH), 11.56 (s, 1H, NH), 7.84 (m, 1H, Ph-H), 7.69 (m, 1H, Ph-H), 7.42 (dd, 2H, J = 15.3, 8.1 Hz, Ph-H), 2.22 (s, 3H, CH_3).

2.2. General synthetic procedures for 1,2,4-triazole thione derivatives

General synthetic procedure for 1-((4-substituted piperazin-1-yl)methyl)-3-(2-fluorophenyl)-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione (**2a–i**): To a solution of 5-(2-fluorophenyl)-4-phenyl-4*H*-1,2,4-trizole-3-thiol **1** (0.27 g, 1 mmol) in anhydrous ethanol (10 mL), 4-substituted piperazine (1 mmol) and 37% formaldehyde (3 mmol) was added, then the resulting solution was stirred at room temperature for 1–2 h. The resulting precipitate was filtered and recrystallized from ethanol and water to give compounds **2a–i**.

General synthetic procedure for 1,1′-(piperazine-1,4-diyl-bis(methylene))bis(3-(2-fluorophenyl)-4-phenyl-1*H*-1,2,4-triazole-5(4*H*)-thione) (**2j**): To a solution of 5-(2-fluorophenyl)-4-phenyl-4*H*-1,2,4-trizole-3-thiol **1** (0.4 g, 1.48 mmol) in anhydrous ethanol (15 mL), anhydrous piperazine (0.06 g, 0.74 mmol) and 37% formaldehyde (4.5 mmol) was added, then the reaction solution was stirred at room temperature for 20 min. The resulting precipitate was filtered and recrystallized from ethanol to give compound **2j**.

General synthetic procedure for *N*-(1-((4-substituted piperazin-1-yl)methyl)-3-methyl-5-thioxo-1*H*-1,2,4-triazol-4(5*H*)-yl)-2/3-fluorobenzamide (**4a-c**, **5a-d**): The procedure was similar to those of **2a–i**. Using *N*-(3-mercapto-5-methyl-4*H*-1,2,4-triazol-4-yl)-2/3-fluorobenzamide (**3**) as trizole material, compounds **4a-c**, **5a-d** were obtained.

2.3. Herbicidal and fungicidal activity test

Herbicidal activity *in vivo* of compounds were determined by rape root test (*Brassica campestris*) and barnyardgrass cup test (*Echinochloa crusgalli*) according to the reported method [24].

Fungicidal activity *in vitro* of the compounds against *Fusarium omysporum*, *Cercospora arachidicola*, *Physalospora piricola*, *Rhizoctonia cerealis*, *Alternaria solani Sorauer* and *Gibberella sanbinetti* were evaluated *via* the mycelium growth rate test according to the literature [15].

3. Results and discussion

3.1. Synthesis and spectra characterization

The synthetic procedures for target compounds **2**, **4** and **5** were shown in Schemes 1 and 2. The Mannich reaction of **1** or **3** with formaldehyde and substituted piperazine in ethanol at room temperature led to novel Mannich bases with high yields in short time. Using 1,2,4-triazole thiol **1**, to react with formaldehyde and various piperazine intermediates which bearing substituted benzyl, or phenyl, or 2-pyridyl, or 4,6-disubstituted pyrimdin-2-yl at 4-position of piperazine, the corresponding 1,2,4-triazole thione derivatives containing various piperazine moieties **2a–i** were successfully synthesized. It is worthy to note that Foks *et al.* prepared the similar compounds from the Mannich reaction of triazole-thiol intermediate with methanol or dioxane as solvent under condition of refluxing (1 h) [13], by contrast, our synthetic procedure during this step for compounds **2a–i** was to carry out the reaction in ethanol at room temperature. Using this method, the target compounds can also be obtained in moderate to excellent yields within 1–2 h, which indicates our synthetic reaction has advantage in some extent and this may be a favorable factor during its possible industrial application. In a 2:1 molar ratio of 1,2,4-triazole thiol **1** and piperazine, novel piperazine-containing bis(1,2,4-triazole thione) **2j** was prepared conveniently in 89% yield using the same procedure. It was also found that the easy synthetic procedure and satisfactory yield for **2j** were similar with those of compounds we reported previously [14], although the substituents at 3- and 4-positions of 1,2,4-triazole were obviously different between two kinds of compounds (3-position: *o*-fluorophenyl *vs.* trifluoromethyl; 4-position: phenyl *vs.* (substituted)benzylideneamino). When arylamide-containing 1,2,4-triazole thiol **3** was used, the Mannich reaction also can occur smoothly to give corresponding thione derivatives **4** and **5**. Comparing with the usual cases that the (substituted)benzylideneamino or aryl at 4-position of 1,2,4-triazole [16,17,25,26], such novel arylamide case expands the application range for the heterocyclic Mannich reaction. It is known that the intermediates **1** and **3** can exist either as a thiol or the thione tautomeric forms or as an equilibrium mixture of both forms owing to the thioamide structure (–NH–C(=S)). In some cases the mercapto group (–SH) took part in nucleophilic reaction and the sulfoether products obtained [27,28]. These results in our experiments indicate the thione isomer undertake the Mannich reaction *via* the N–H at α-position of thiocarbonyl (C=S). Overall these Mannich reactions for such kind of structures (including bis(triazole thione) derivative) exhibit noticeable advantages, such as mild reaction condition, high yield and short reaction time, which may be useful factors for possible application during the development of novel agrochemicals.

The target compounds were identified by melting point, IR, ^{1}H NMR and ^{13}C NMR spectra. The measured elemental analyses were also consistent with the corresponding calculated ones (see Supporting information). In ^{1}H NMR, the resonance signals of CH_2 protons neighboring to the triazole ring were observed at δ 5.30–5.40 in Mannich bases **2**, while at δ 5.10–5.15 in Mannich