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Original article

Synthesis and antimicrobical evaluation of a novel class of 1,3,4-thiadiazole: Derivatives bearing 1,2,4-triazolo[1,5-*a*] pyrimidine moiety

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ABSTRACT

A series of novel 1,3,4-thiadiazole derivatives bearing 1,2,4-triazolo[1,5-*a*]pyrimidine moiety were synthesized by the method of splicing active substructures. Among these derivatives, compounds **12**, **13**, **15**–**22** and **24**–**31** were firstly reported. All the compounds were assayed for antimicrobial activities against five fungi strains and four bacteria strains. The preliminary results indicated that compounds **25** and **28**–**31** showed good antifungal activities against *Physaclospora piricola* and *Rhizoctonia solani*. Compound **26** exhibited good antifungal activities against *Cercospora beticola* and *R. solani*. Most of the compounds showed better antibacterial activities against Gram-negative bacteria strains than Gram-positive bacteria strains. Compounds **25** and **28** showed the best activities against *Pseudomonas fluorescence* while compounds **30**–**31** showed good activities against *Escherichia coli*.

1. Introduction

Recently, some publications reported the multidrug-resistant (MDR) bacteria and fungi drastically impaired the efficacy of antimicrobial agents and limited their clinical uses [1–4]. The emergence of Gram-negative Enterobacteriaceae with resistance to carbapenem conferred by New Delhi metallo-β-lactamase 1 (NDM-1) had drawn global attention [5]. Due to the reason, the exploration of novel antibacterial agents or the improvement of previous reported drugs is crucial to overcome MDR infections [6].

Synthesis and biological activities of novel heterocyclic compounds bearing triazolopyrimidine moiety have been studied widely for many years [7–11]. Some were demonstrated as A_{2a} and A_3 receptor ligands [7,8]. Some were potent and selective dihydroorotate dehydrogenase inhibitors with antimalarial activity [9]. Many acetolactate synthase-inhibiting herbicides, such as florasulam, were triazolopyrimidine-2-sulfonamide derivatives while some derivatives exhibited antifungal activity [10,11]. On the other hand, thiadiazole derivatives were also widely applied in the fields of pesticides and medicines because of their strong biological activities [12–14]. Some derivatives were synthesized as potential anti-infective, anti-inflammatory and antiproliferative agents [12,13]. Many derivatives also had antifungal activity [14]. Besides, some derivatives combining both 1,3,4-thiadiazole and 1,2,4-triazole moieties had been reported to have various biological activities such as anticancer, antitubercular, anti-inflammatory, analgesic or anticonvulsant activities [15–20], especially antimicrobial activity [21–23].

In our previous study, we had introduced 1,2,4-triazole moiety into 1,2,4-triazolo[1,5-*a*]pyrimidine moiety and got novel lead compounds with fairly good antifungal activity [24]. In this paper, in order to study the biological activities of diheterocyclic compounds containing 1,2,4-triazolo[1,5-*a*]pyrimidine and 1,3,4-thiadiazole moieties and to find potential antimicrobial activities, we have connected these two moieties using thioether bond by the method of splicing active substructures. Thus, a series of novel 1,3,4-thiadiazole derivatives bearing 1,2,4-triazolo[1,5-*a*]pyrimidine moiety were synthesized. Their antibacterial activities against *Escherichia coli*, *Pseudomonas fluorescence*, *Bacillus subtilis* and *Staphylococcus aureus*, and antifungal activities against *Fusarium oxysporum* f.sp. *vasinfectum*, *Gibberella sanbinetti*, *Cercospora beticola* Sacc, *Physaclospora piricola* and *Rhizoctonia solani* were evaluated. The results of this study might be useful to researchers attempting to find new potential antimicrobials.

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2. Results and discussion

2.1. Chemistry

This series of novel 1,3,4-thiadiazole derivatives bearing 1,2,4-triazolo[1,5-*a*]pyrimidine moiety were synthesized according to the synthetic route outlined in Scheme 1.

The precursor, 2-(5,7-dimethyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-ylthio)acetohydrazide, compound **6**, was prepared via five steps which began with hydrazine hydrate, according to the reported method [24,25]. The synthesized **6** was then dissolved in ethanol and reacted with carbon disulfide (CS_2) at the presence of potassium hydroxide (KOH) to afford compound **7**. After that compound **10**, was obtained from **7** via three steps as white powder.

Target compounds **11**–**31**, 1,3,4-thiadiazole derivatives bearing 1,2,4-triazolo[1,5-*a*]pyrimidine moiety, were synthesized by nucleo philic substitution reaction of compound **10** and halogen compounds as shown in Scheme 1. Among these compounds, **12**, **13**, **15**–**22** and **24**–**31** were firstly reported.

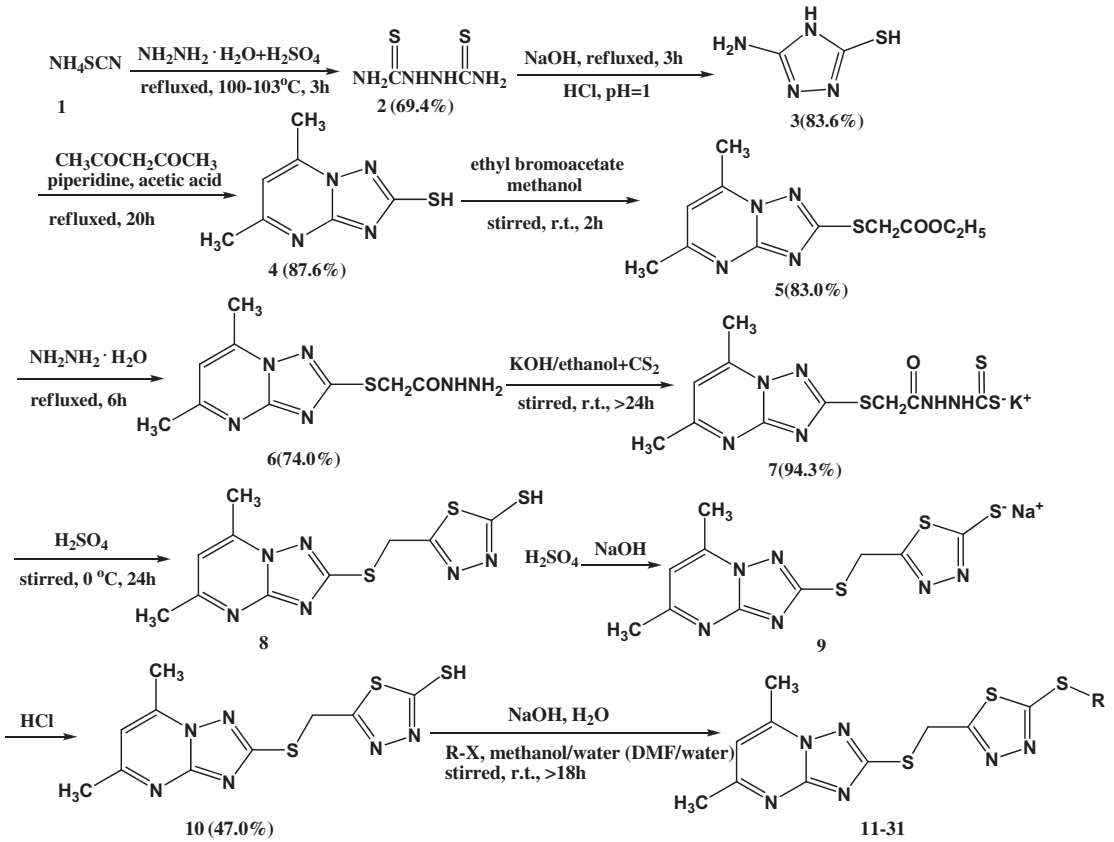
The structure elucidations of the newly synthesized compounds were carried out by different spectroscopic techniques like ^{1}H NMR, ^{13}C NMR and EI-MS. Further confirmations of the compounds were carried out by elemental analysis (±0.4%). The elemental analysis data and some physical properties of these compounds were reported in Table 1.

2.2. Antifungal activity

The antifungal activities of compounds **11**–**31** against *Fusarium vasinfectum*, *G. sanbinetti*, *C. beticola*, *P. piricola* and *R. solani* were evaluated by our previous method [24]. Three commercial fungicides triadimefon, validamycin and carbendazim were selected as positive controls. The results were summarized in Table 2.

The results showed that most of the synthesized compounds exhibited good antifungal activities except **15** and **23**, however, all the compounds showed different activities against different fungi strains. For example, most compounds showed very good inhibitory activities against *P. piricola* and activities of **11**–**14**, **16**, **18**–**21**, **24**, **25** and **28**–**31** could be comparable with Grade B (inhibition rate = 70%–89%). Many compounds showed good antifungal activities against *R. solani*, such as **25**–**31**, however, only several compounds (**17**, **22** and **26**) showed good inhibitory activities against *C. beticola*. The inhibitory activities of these compounds against *F. oxysporum* and *G. sanbinetti* were rather poor and only the activity of **24** against *G. sanbinetti* was comparable with Grade B. On the other hand, many compounds, whose activities were comparable with Grade B, showed good inhibitory activities on two fungi strains. **25** and **28**–**31** showed good activities against *P. piricola* and *R. solani* while **26** showed good activities against *C. beticola* and *R. solani*. The compounds, whose activities could be comparable with Grade B, were more potent than that of positive controls.

As previously reported, 1,2,4-triazolo[1,5-*a*]pyrimidine derivatives exhibited many biological activities [7–11]. The triazolopyrimidine structure including the S atom, which is a large delocalized electron-rich system, might play an important role in the various activities. The biological activities were possibly related to the spatial orientation and electron donating capacity of the triazolopyrimidine [25]. On the other hand, thiadiazole derivatives had strong antifungal activity. The antifungal effect was mainly caused by an activation of phospholipases in the mitochondrial



Scheme 1. Synthesis of target compounds **11**–**31**. If R–X was liquid under room temperature, methanol/water was used as mixed solvent; if R–X was solid, DMF/water was used.