Bioorganic & Medicinal Chemistry Letters 26 (2016) 1849–1853

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and bioactivities of novel piperazine-containing 1,5-Diphenyl-2-penten-1-one analogues from natural product lead

Gaofei Xu [a], Xinling Yang [a], Biaobiao Jiang [a], Peng Lei [a], Xili Liu [b], Qingmin Wang [c], Xuebo Zhang [a], Yun Ling [a,*]

[a] Department of Applied Chemistry, College of Science, China Agricultural University, Beijing 100193, China
[b] Department of Plant Pathology, College of Agronomy and Biotechnology, China Agricultural University, 100193, China
[c] State Key Laboratory of Elemento-Organic Chemistry, Research Institute of Elemento-Organic Chemistry, Nankai University, Tianjin 300071, China

ARTICLE INFO

Article history:
Received 6 November 2015
Revised 20 January 2016
Accepted 30 January 2016
Available online 13 February 2016

Keywords:
1,5-Diphenyl-2-penten-1-one
Stellera chamaejasme L.
Piperazine
Synthesis
Bioactivities

ABSTRACT

A series of novel 1,5-Diphenyl-2-penten-1-one analogues (**7a**–**h**, **8a**–**h**) with piperazine moiety have been designed and synthesized on the basis of natural product 1,5-Diphenyl-2-penten-1-one (**I**). All the synthesized compounds were evaluated in vitro for anti-plant pathogenic fungi activities and insecticidal activities. The results indicated that most of these analogues exhibited moderate antifungal activities and moderate to good insecticidal activities. Amongst them, the most potent **7c**, **7e** and **7h** keep a mortality of 100% against larva of mosquito at the concentration of 1 mg/L. Initial structure–activity relationship (SAR) analysis showed that, a methyl group can influence the biological activities of these compounds significantly, the compounds with *N*′-unsubstituted piperazine showed much better antifungal activities and larvicidal activity against mosquito than the compounds with *N*′-methylated piperazine. In addition, the larvicidal activity against mosquito had sharply decline when the substituent on benzene ring was changed from 4-position to 2 or 3-position.

Natural products are often used as lead structures for the discovery of novel pesticides despite of their low yield, instability, and limited biological activities.[1–3] Meanwhile, there are many advantages of botanical pesticides produced from natural products, such as less or slower resistance development and lower environmental pollution. Therefore, the discovery of new pesticides directly or indirectly originated from natural products has recently been crucial in the search of agrochemicals and attracted much research attention.[4–6] 1,5-Diphenyl-2-penten-1-one (**I**) and 1,5-Diphenyl-1-pentanone(**II**) (Fig. 1) were first isolated from *Stellera chamaejasme* L. (Thymelaeaceae, used in Chinese traditional medicine) by Hou et al. in 2001.[7] These two natural products are similar in structure to daphneolone, a nematicidal substance extracted from *Daphne odora*.[8] Laboratory bioassay showed that these two compounds had strong contact activity and very good antifeedant activity against *Aphis gossypii* and *Schizaphis graminum*.[9,10] Moreover, compound **I** exhibited the similar effects on ATP-ase found in the three membranes amongst which the plasma membrane Ca^{2+}-Mg^{2+}-ATPase is the primary target.[11] After that, by replacing the two benzene ring of compound **I** with different aromatic C_6 and C_5 aromatic rings or changing the bridge chain, various analogues with antifungal activity and insecticidal activity were synthesized by Hou's group and our group.[12–17] However, by the conservative approach of modification, the improvement of the bioactivity of most analogues was limited. Thus, further study is required to develop new potential pesticide molecules with enhanced bioactivity and safety to humans and the environment.

Heterocycles play important roles in medical chemistry and agrochemicals, such as pyridine, pyrazole, triazole, thiophene. Amongst them, piperazine is a very important starting material in the pharmaceutical industry. Piperazine derivatives have been experimented extensively by the organic chemists due to the derivatives' close association with various types of biological properties, such as antiviral,[18] antibacterial,[19] anticancer,[20] anti-HIV,[21] antimalarial,[22] antifungal[23] and so on.[24,25] Piperazine itself as well

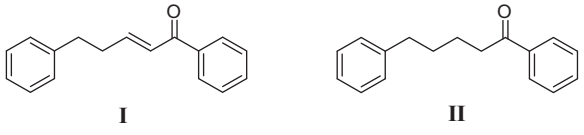


Figure 1. The chemical structure of compound **I** and **II**, originally isolated from *Stellera chamaejasme* L.

* Corresponding author.

http://dx.doi.org/10.1016/j.bmcl.2016.01.088
0960-894X/

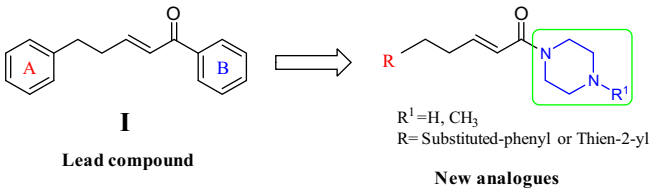


Figure 2. Design strategy of titled compounds.

as 1-methylpiperazine are symmetric, commercially available, inexpensive compounds, which makes their synthetic elaboration for agrochemicals attractive. However, there are few commercial pesticides with piperazine moieties in the structure.

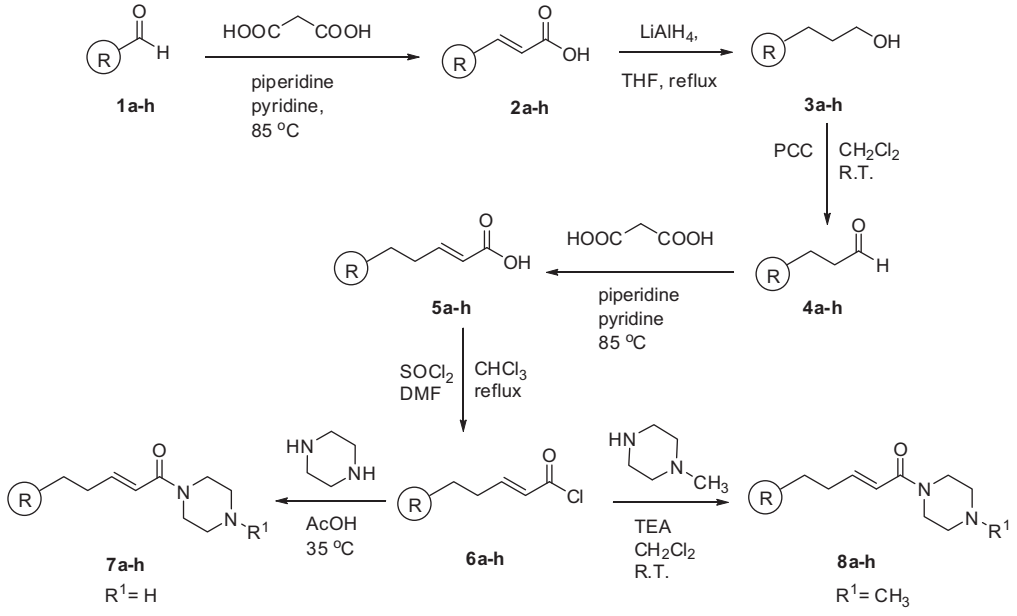
In view of the need of potent and environmental friendly agrochemicals and in continuation of our earlier interest in this field,[15–17] here a series of new analogues were designed by introducing unsaturated piperazine moiety to replace B-ring of lead compound I and replacing A-ring with substituted phenyl or thiophene ring with the aim to obtain new products with simple structure and good activities (Fig. 2). All the compounds were evaluated for the activities against five plant pathogenic fungi and four kinds of insects (larvae of mosquito, armyworm, cotton bollworm and corn borer). In addition, the initial SAR analysis was also reported in the present work.

The synthetic route of title compounds **7a**–**h**, **8a**–**h** is shown in the Scheme 1. Initially, substituted cinnamic acids **2** were synthesized by a knoevenagel reaction of substituted benzaldehydes **1** with malonic acid in the presence of piperidine in pyridine, according to the method in the literature.[26] Next, following the procedure described in the literature,[27] substituted cinnamic acids **2** were reduced by lithium aluminium hydride to afford substituted phenylpropanol **3**. Then **3** were oxidised by PCC, leading to the corresponding substituted benzenepropanal **4**. (*E*)-5-(Substituted phenyl) pent-2-enoic acid **5** were obtained through the same process as compound **2**. Finally, target compounds **7** were prepared by the acylchlorination of compound **5** followed by a condensation reaction with piperazine in acetic acid as solvent. While target compounds **8** were synthesized by the acylchlorination of compound **5** followed by a condensation reaction with 1-methylpiperazine in the presence of triethylamine.

The synthesized **7a**–**h**, **8a**–**h** were evaluated for their fungicidal activities against five plant pathogenic fungi (*Pythium aphanidermatum*, *Sclerotinia sclerotiorum*, *Botrytis cinerea*, *Alternaria solani* and *Bipolaris maydis*) first at the concentration of 50 mg/L according to the method in the references.[28] Difenoconazole, a commercial fungicide, was used as a positive control. The results were reported in Table 1. Data listed in Table 1 showed that most of the tested compounds exhibited fungicidal activities at a moderate level. Some compounds showed superior activities against *Pythium aphanidermatum* and *Botrytis cinerea* than lead compound **I**. Amongst them, the inhibitory rates of **7b**, **7f** and **7g** against *Pythium aphanidermatum* reached 57.5%, 58.9% and 58.2%, respectively, similar with difenoconazole (58.9%). However, for the rest plant pathogenic fungi, most compounds did not show better activities compare with difenoconazole and compound **I**. Interestingly, The methyl group on *N*′-position of piperazine has a significant influence on their fungicidal activity, especially against *Pythium aphanidermatum*, *Botrytis cinerea* and *Alternaria solani* (Fig. 3). After N-methylation of **7a**–**h**, namely compounds **8a**–**h**, almost all the fungicidal activities declined sharply. One possible reason maybe the N-methylation changed the Log P of the compounds and ultimately affected their penetrability. Moreover, the introduction of thiophene group (**7e**, **8e**) is unfavorable to the fungicidal activity.

Further EC_{50} value of some compounds (**7a**, **7b**, **7f**, **7g**, **8a**, **8b**, **8f**, **8g**) against *Pythium aphanidermatum* were then tested (Table 2). Compound **7g**, with a 3-position chlorine substituted phenyl group, exhibited the highest activity with an EC_{50} of 0.075 mM, superior to compound **I** (0.39 mM). Moreover, same with the above result, the fungicidal activities of compound with *N*′-unsubstituted piperazine (**7a**, **7b**, **7f**, **7g**) were much better than compounds with *N*′-methyl piperazine (**8a**, **8b**, **8f**, **8g**).

Considering that compound **I** has insecticidal activities and the various activities of piperazine moiety, we then tested the insecticidal activities against four kinds of insects (larvae of mosquito (*Culex pipiens pallens*), armyworm (*Mythimna separate*), cotton bollworm (*Helicoverpa armigera*) and corn borer (*Ostrinia nubilalis*))



Scheme 1. Synthetic route for 1,5-Diphenyl-2-penten-1-one analogues **7a**–**h**, **8a**–**h**.