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

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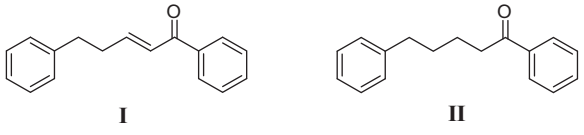
ABSTRACT

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



I II

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

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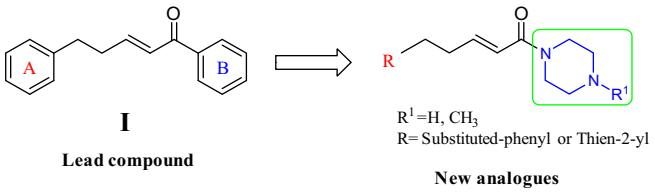


Figure 2. Design strategy of titled compounds.

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.

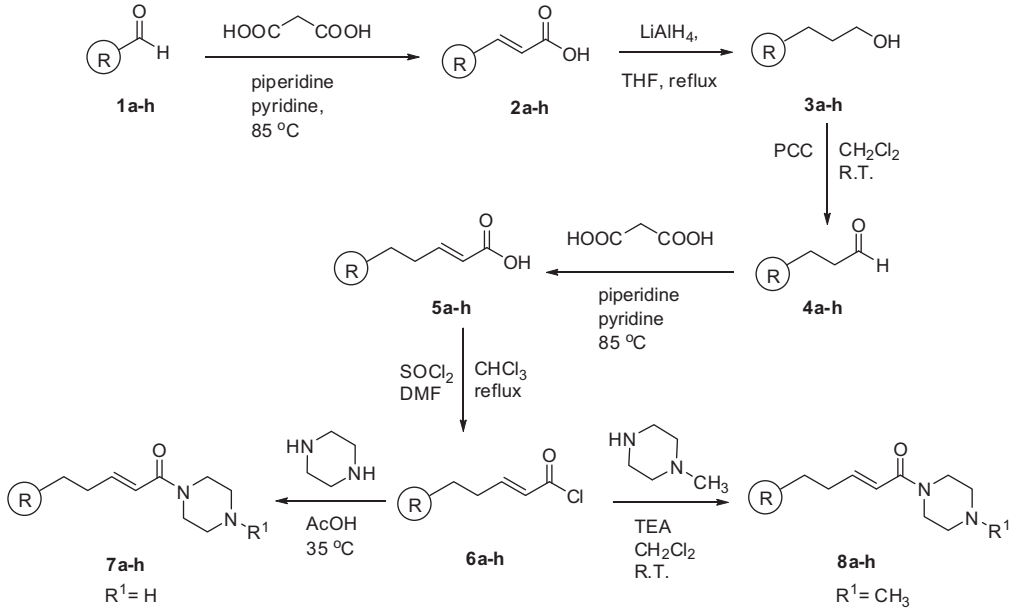
In view of the need of potent and environmental friendly agrochemicals and in continuation of our earlier interest in this field,[15–17] here a series of new analogues were designed by introducing unsaturated piperazine moiety to replace B-ring of lead compound I and replacing A-ring with substituted 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**.

Table 1
The in vitro antifungal activities of title compounds **7a–h**, **8a–h**[a]

Compd	R	R^1	*C*Log *P*[c]	Inhibitory %				
				P. aphanidermatum	*S. sclerotiorum*	*B. cinerea*	*A. solani*	*B. maydis*
7a	Ph	H	1.36	30.8	25.0	24.6	28.1	18.6
7b	4-CH_3-Ph	H	1.84	57.5	19.3	13.0	16.5	27.5
7c	4-CH_3O-Ph	H	1.38	23.6	20.9	9.9	0.0	17.1
7d	4-C_2H_5O-Ph	H	1.74	26.8	21.3	32.5	16.5	15.6
7e	Thiophene-2-yl	H	1.17	10.9	8.6	21.0	13.8	6.3
7f	2-Cl-Ph	H	1.80	58.9	21.7	46.7	20.5	35.4
7g	3-Cl-Ph	H	2.08	58.2	11.5	22.8	19.6	20.6
7h	4-Cl-Ph	H	2.13	22.5	7.4	15.7	14.7	24.5
8a	Ph	CH_3	1.72	8.1	27.5	0.0	12.4	9.2
8b	4-CH_3-Ph	CH_3	2.20	16.3	16.0	15.2	7.9	20.6
8c	4-CH_3O-Ph	CH_3	1.75	8.4	34.8	5.5	10.2	9.2
8d	4-C_2H_5O-Ph	CH_3	2.10	8.4	26.6	0.0	13.8	22.0
8e	Thiophene-2-yl	CH_3	1.54	7.7	32.8	0.0	0.0	5.8
8f	2-Cl-Ph	CH_3	2.16	8.1	32.8	0.0	0.0	36.3
8g	3-Cl-Ph	CH_3	2.44	16.0	26.2	0.0	0.0	28.5
8h	4-Cl-Ph	CH_3	2.49	11.3	27.5	0.0	0.0	42.8
Compound **I**	/	/	/	27.5	50.0	14.3	27.7	44.7
DZ[b]	/	/	/	58.9	96.7	73.4	95.5	94.6

[a] Were measured at concentration of 50 mg/L.
[b] DZ means difenoconazole, used as the positive control.
[c] Log*P* means octanol-water partition coefficient, which is equal to the logarithm of the ratio of concentrations of an unionized compound between octanol and water. *C*log*P* is a calculated log*P* value in silico method.

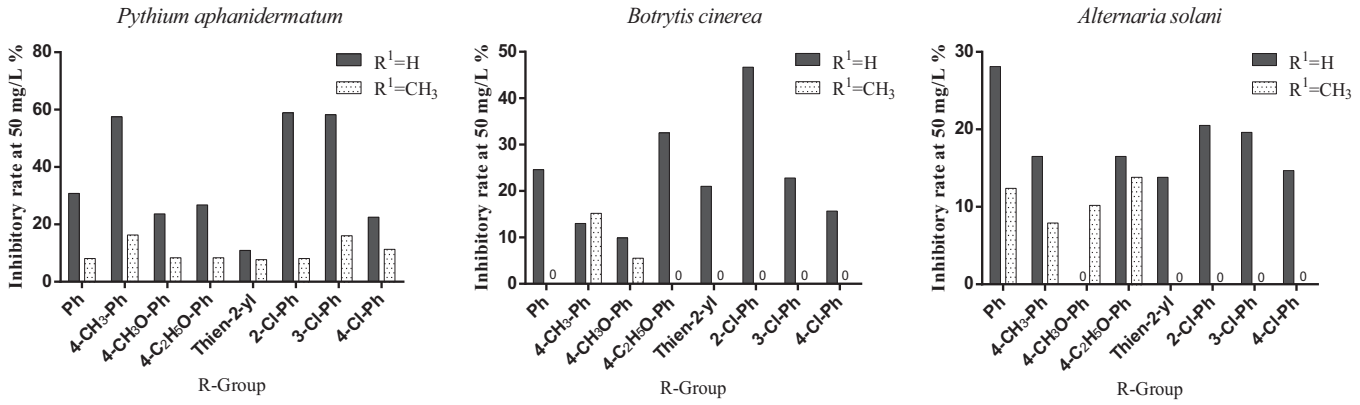


Figure 3. The effect of methyl on the fungicidal activities of title compounds.

Table 2
The EC_{50} value of some title compounds against *Pythium aphanidermatum*

Compd	EC_{50} (mM)	Compd	EC_{50} (mM)
7a	0.48	**8a**	>2
7b	0.14	**8b**	>2
7f	0.10	**8f**	0.82
7g	0.075	**8g**	0.85
Compound **I**	0.39	/	/
Difenoconazole	0.075	/	/

of all the titled compounds using reported methods.[29] The results were listed in Tables 3 and 4.

Data in Table 3 showed that most of the compounds exhibited good to excellent larvicidal activity against mosquito (*Culex pipiens pallens*) at given concentrations (10, 5, 2, 1, 0.5 mg/L), and the most potent compounds **7c**, **7e** and **7h** still keep a mortality of 100% when the concentration reduced to 1 mg/L, which is much better than that of lead (**I**). Just like fungicidal activity, when the R-ring is same, the larvicidal activity of all the compounds with *N*′-unsubstituted piperazine were obviously higher than that of the compounds containing *N*′-methyl piperazine moiety. For instance, the activities of **7c**, **7e**, **7h** had a 100% morality at the concentration of 1 mg/L, whereas the activities of **8e**, **8h** were 20% and 60%, respectively, and **8c** had no activity at the same concentration.

The positions of the substituents on the benzene ring also had a significant influence on the larvicidal activity against mosquito. For instance, compound **7h** and **8h**, with chlorine substituent on the 4-position, exhibited obvious activities (100% and 60%, respectively, at 1 mg/L). However, compound **7f**, **7g**, **8f** and **8g**, with chlorine substituent on the 3-position or 2-position, had no activity at the concentration of 5 mg/L). Moreover, unlike fungicidal activity, when R is thiophene ring, the compounds (**7e**, **8e**) exhibited higher larvicidal activity against mosquito than those compounds with unsubstituted phenyl ring as R-ring (**7a**, **8a**).

Some of these synthesized compounds also showed moderate to good insecticidal activities against cotton bollworm (*Helicoverpa armigera*), corn borer (*Ostrinia nubilalis*) and armyworm (*Mythimna separate*) at the concentration of 600 mg/L (Table 4). Amongst them, **8b** and **8c**, which contain 4-position methyl substituted phenyl group and 4-position methoxy substituted phenyl group respectively, showed better activities (60%, 55%, respectively) against *H. armigera* than that of lead compound **I** (15%). **7b**, **7e**,

Table 3
Larvicidal activity against mosquito of title compounds

Compd	R	R^1	% mortality at given concentration				
			10 mg/L	5 mg/L	2 mg/L^{-1}	1 mg/L	0.5 mg/L
7a	Ph	H	100	100	60	–	–
7b	4-CH_3-Ph	H	100	100	100	60	–
7c	4-CH_3O-Ph	H	100	100	100	100	50
7d	4-C_2H_5O-Ph	H	100	100	100	60	–
7e	Thiophene-2-yl	H	100	100	100	100	20
7f	2-Cl-Ph	H	70	–[b]	–	–	–
7g	3-Cl-Ph	H	70	–	–	–	–
7h	4-Cl-Ph	H	100	100	100	100	10
8a	Ph	CH_3	100	0	–	–	–
8b	4-CH_3-Ph	CH_3	100	20	–	–	–
8c	4-CH_3O-Ph	CH_3	100	0	–	–	–
8d	4-C_2H_5O-Ph	CH_3	100	100	60	–	–
8e	Thiophene-2-yl	CH_3	100	100	100	20	–
8f	2-Cl-Ph	CH_3	50	–	–	–	–
8g	3-Cl-Ph	CH_3	40	–	–	–	–
8h	4-Cl-Ph	CH_3	100	100	100	60	–
Compound **I**	/	/	100	0	–	–	–
Diflubenzuron[a]	/	/	100	0	–	–	–

[a] Diflubenzuron was used as the positive control.
[b] Not keep tested when mortality was lower than 100%.

Table 4
Insecticidal activities against *H. armigera*, *O. nubilalis* and *M. separata* of title compounds

Compd	R	R^1	Insecticidal activity (% mortality)		
			H. armigera 600 mg/L	*O. nubilalis* 600 mg/L	*M. separata* 600 mg/L
7a	Ph	H	35	45	50
7b	4-CH_3-Ph	H	50	60	70
7c	4-CH_3O-Ph	H	25	40	10
7d	4-C_2H_5O-Ph	H	30	50	40
7e	Thiophene-2-yl	H	50	70	35
7f	2-Cl-Ph	H	25	50	5
7g	3-Cl-Ph	H	30	50	20
7h	4-Cl-Ph	H	35	35	70
8a	Ph	CH_3	15	15	50
8b	4-CH_3-Ph	CH_3	60	35	80
8c	4-CH_3O-Ph	CH_3	55	65	65
8d	4-C_2H_5O-Ph	CH_3	30	45	25
8e	Thiophene-2-yl	CH_3	40	70	5
8f	2-Cl-Ph	CH_3	10	15	20
8g	3-Cl-Ph	CH_3	50	65	65
8h	4-Cl-Ph	CH_3	15	15	25
Compound **I**	/	/	15	10	20
Diflubenzuron[a]	/	/	65	50	100

[a] Diflubenzuron was used as the positive control.

8c, **8e**, **8g**, had much higher activities (60%, 70%, 65%, 70%, 65%, respectively) against *Ostrinia nubilalis* than that of compound **I** (10%). Also, the activities against *Mythimna separata* of **7b**, **7h**, **8b**, **8c**, **8g** were 70%, 70%, 80%, 65%, 65%, respectively, obviously better than the lead compound (20%). What is more, **7b**, **8c** and **8g**, containing a 4-position methyl substituted phenyl group, 4-position methoxy substituted phenyl group and 3-position chlorine-substituted phenyl group, respectively, exhibited broad spectrum insecticidal activities against these three kinds of insects, which is worthy to be further studied.

In conclusion, A series of novel 1,5-Diphenyl-2-penten-1-one analogues with piperazine moiety have been designed and synthesized on the basis of natural product **I** from *Stellera chamaejasme* L. The bioassay results indicated that some compounds exhibited fungicidal activities at the concentration of 50 mg/L at a moderate level. Amongst them, the EC_{50} value of the compounds **7b**, **7f**, **7g** against *Pythium aphanidermatum* were 0.14 mM, 0.10 mM and 0.075 mM, respectively, superior to that of the lead compound **I**. What is more, most of these analogues exhibited moderate to good insecticidal activities. Particularly, the most potent compounds **7c**, **7e** and **7h**, keep a mortality of 100% against larvae of mosquito at the concentration of 1 mg/L, are promising new agents for prevention and control of mosquito. Initial SAR study showed that, when the R-ring is same, the antifungal activities and larvicidal activity against mosquito of the compounds with *N′*-unsubstituted piperazine were better than that of the compounds with *N′*-methyl 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. These results are worthy for study on new pesticides discovery. Further studies on structural optimisation are in progress in our laboratory.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2016.01.088.

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Bioassay of fungicidal activities: The tested compounds were dissolved in DMSO to prepare the 10 mg/mL stock solution before mixing with PDA (Potato Dextrose Agar) medium under 50 °C. The medium containing compounds at a concentration of 50 mg/L for the initial screening was poured into sterilized Petri dishes. After the dishes were cooled, the mycelia disks of 7 mm diameter were inoculated in the center of the Petri dishes and incubated at 25 °C for 2–3 d. Each experiment was carried out in triplicates. The mixed medium without sample was used as the blank control. The colony diameter of each strain was measured by cross bracketing method after 2–3 d of culture. The inhibition rate was calculated according to the following formula: Inhibition rate (%) = $(C - T)/(C - 7\ \text{mm}) \times 100\%$. Here, C is the average diameter (in mm) of mycelia in the blank test. T is the average diameter (in mm) of mycelia on treated PDA with tested compounds.
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Larvicidal activity against mosquito: The immersion method assay was used for Culex pipiens pallens tests, the title compounds were prepared to a terminal concentration of 10–0.5 mg/L by dissolving them in acetone and adding distilled water. Ten fourth-instar mosquito larvae were put into the 10 mL of the test solution and raised for 8 days; the results were expressed by death percentage, the bioassay was repeated in triplicate. Insecticidal activities against Oriental Armyworm (Mythimna separate), Cotton Bollworm (Helicoverpa armigera), Pyrausta Nubilalis (Ostrinia nubilalis): The stomach toxicities of the title compounds against oriental armyworm, cotton bollworm, pyrausta nubilalis were evaluated by foliar application. Individual corn leaves were placed on moistened pieces of filter paper in Petri dished. The leaves were then sprayed with the test solution and allowed to dry. The dishes were infested with 10 fourth-instar larvae. Percentage mortalities were evaluated 2 days after treatment. Each treatment was performed three times.