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Research Article



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# Design, Synthesis, and Bioactivities Screening of a Diaryl Ketone-Inspired Pesticide Molecular Library as Derived from Natural Products

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**Three natural products, 1,5-diphenylpentan-1-one, 1,5-diphenylpent-2-en-1-one, and 3-hydroxy-1,5-diphenylpentan-1-one, with good insecticidal activities were extracted from *Stellera chamaejasme* L. Based on their shared diaryl ketone moiety as 'pharmacophores', a series of diaryl ketones were synthesized and tested for insecticidal activity, acetylcholinesterase inhibitory activity, and antifungal activity. All synthesized compounds showed poor insecticidal and acetylcholinesterase inhibitory activities. Compound III with a furyl ring showed strong activities against plant pathogenic fungi. The $IC_{50}$ of compound (*E*)-1-(2,4-dichlorophenyl)-3-(furan-2-yl)- -prop-2-en-1-one ($III_2$) was 1.20 mg/L against *Rhizoctonia solani*, suggesting its strong potential as a novel antifungal drug.**

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**Key words:** antifungal activity, bioactivity, diaryl ketones, pesticide, synthesis

The identification of efficient pesticides is the central topic of agrochemical research. The discovery of novel modulators of protein function lies in the identification of appropriate starting points in chemical structure for compound library development, which could serve as 'leitmotifs' for the synthesis of biologically relevant compounds. New strategies for library design now are focused on natural product guiding (1–5), protein structure, and biologic or diversity orientation (6–18) to gain access to reveal novel chemical structures.

Natural products can be regarded as evolutionarily selected ligands for ligand-sensing cores of proteins. They emerge via biosynthesis by proteins and often fulfill various biologic functions through interaction with multiple proteins (19,20). Their underlying structures define structural prerequisites for binding to proteins and biologic activity. Because the entire biologically relevant chemical space may be larger than the structural space occupied by natural products, their structural scaffolds represent the biologically relevant and prevalidated fractions of chemical structure space explored by nature so far. Consequently, compound collections designed to mimic the structure and property of natural products will have greater biologic relevance than the libraries obtained on the basis of chemical feasibility alone. Therefore, natural products–guided compound library development should follow this guiding principle for pesticides identification in agrochemical research (1,19–22) (Figure 1).

Our group is devoted to the discovery, synthesis, and screening of new pesticides. *Stellera chamaejasme* L. (Thymelaeaceae) is one type of toxic Chinese herb. The root is used as 'Langdu' in traditional Chinese medicine. It displays therapeutic effects on some diseases such as leucocythemia and stomach cancer (23). In recent years, its insecticidal activity against some pests has drawn wide attention (24,25). 1,5-diphenylpentan-1-one (compound **a**), 1,5-diphenylpent-2-en-1-one (compound **b**), and 3-hydroxy-1,5-diphenylpentan-1-one (compound **c**) are isolated from *S. chamaejasme* L. Laboratory bioassays showed that compounds **a** and **b** had strong contact activities and very good antifeedant activities against *Aphis gossypii* and *Schizaphis graminum* (26). Contact activities ($LC_{50}$) of compounds **a** and **b** against aphids were 443 and 195 mg/L, respectively, and the antifeedant activities ($LC_{50}$) of compounds **a** and **b** on aphids were 462 and 383 mg/L, respectively. Moreover, at a dose of 2 g/kg *per os*, the two compounds did not cause any toxic effects in mice, rats, or rabbits. Furthermore, compound **b** showed an 83.6% inhibition against $Ca^{2+}$-$Mg^{2+}$-ATPase at 20 $\mu$mol/L and a 70% inhibition against acetylcholinesterase (AChE) at $5 \times 10^3$ mg/L. Compound **c** acted on AChE with an inhibition ratio of 78.5% at 162 mg/L (27,28).

A systematic study on the diaryl ketone compounds **a**, **b**, and **c** revealed that the analogs bearing only aryl, no aryl, or no ketone

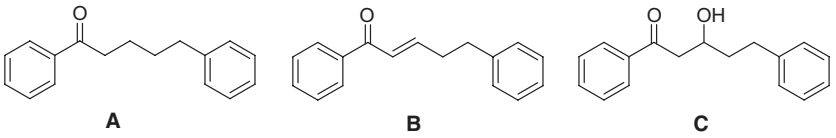



**Figure 1:** Compounds **a, b**, and **c** from *Stellera chamaejasme* L.

moieties instead of diaryl ketone moiety show poor biologic activity. Thus, we hypothesized that the diaryl ketone moiety might represent a 'privileged' pharmacophore structure, which conveyed biologic relevance to compound collections derived thereof. In this study, a compound collection with a diaryl ketone moiety as the 'pharmacophore' has been synthesized. Their insecticidal and antifungal activities have been examined in an effort to reveal their potential use in agrochemistry.

## Materials and Methods

### *Reagents and analysis*

All chemicals and solvents purchased from commercial sources were used without specific purification. $^1$H NMR spectra were recorded in a deuterochloroform solution on a Bruker spectrometer (400 MHz; Bruker, Fallanden, Switzerland), using tetramethylsilane as an internal standard.

### *Synthesis*

#### General procedure for synthesis of diaryl ketones

An appropriately substituted acetophenone (10 mmol) was added to equimolar quantities of appropriate aryl aldehyde, furfural, or cinnamaldehyde in EtOH (10 mL). Then, an aqueous solution of NaOH (2%, 3 mL) was added, and the reaction mixture was stirred for 5 h and then refrigerated overnight. The product crystals were filtrated and washed carefully with water and cold EtOH. The resulting product was purified by recrystallization.

### *Bioactivity*

#### Insecticidal activity examination

The aphid colony was reared on cotton plants in the greenhouse. They were maintained at 22–23 °C with a 14:10 h (light:dark) photoperiod. Vigorous and apterous aphids (4-day-old aphids) were used in the experiments. To obtain 4-day-old aphids, adult cotton aphids were transferred to cotton plants and allowed to deposit nymphs overnight, and then the adult aphids were removed. Four days later, the resulting aphids were collected for the bioassays.

Bioassays of fungicidal activity were performed following products as previously described (29). Bioassays were carried out at room temperature (20–21 °C) in petri dishes (15 cm diameter). Solutions of the test products and omethoate (standard) were separately prepared in acetone:water:polysorbate 80 (1:9:0.01% by volume) with varied compound concentrations. Fresh cotton leaves were immersed in the solutions and allowed to air dry in the petri dishes. Healthy and apterous aphids were gently dislodged from the undersides of leaves onto the treated leaves. Fifty aphids were subjected to each bioassay, and the entire experiment was replicated three times. Control leaves were treated only with the solvent. The number of dead aphids was recorded after 48 h to calculate the mortality rate (%), which was corrected for control mortality by Abbott's formula.

#### Enzyme activity

The capacity of all compounds $\mathbf{I_{1–46}}$, $\mathbf{II_{1–14}}$, and $\mathbf{III_{1–15}}$ to inhibit AChE activity was assessed using Ellman's method (30). Acetylcholinesterase (E.C. 3.1.1.7, from *electric eel*), 5,5′-dithiobis-(2-nitrobenzoic acid; DTNB, Ellman's reagent), butylthiocholine chloride, acetylthiocholine chloride, and tarcine hydrochloride were purchased from Sigma-Aldrich (St. Louis, MO, USA).

The tested compounds were dissolved in Tween 80/MeOH 3:1 (v/v, <400 L total volume) and were diluted in 0.1 M $KH_2PO_4/K_2HPO_4$ buffer (pH 8.0) to provide a final concentration. Tween 80/MeOH was diluted to a concentration in excess of 1 in 1250, and no inhibitory action on AchE was detected in separate prior experiments.

*In vitro* AChE assay. All the assays were carried out under 0.1 M $KH_2PO_4/K_2HPO_4$ buffer, pH 8.0, using a Shimadzu UV-2450 spectrophotometer (Kyoto, Japan). Enzyme solutions were prepared to give 2.0 units/mL in 2 mL aliquots. The assay medium (1 mL) contained phosphate buffer (pH 8.0), 50 mL of 0.01 M DTNB, 10 mL of enzyme, and 50 mL of 0.01 M substrate (Acetylthiocholine chloride solution). The substrate was added to the assay medium containing the compound solution, enzyme, buffer, and DTNB with inhibitor after a 15-min incubation. Activity was determined by measuring the increase in absorbance at 412 nm at 1 min intervals at 37 °C. Calculations were performed according to the equation in Ellman *et al*. Each concentration was assayed in triplicate.

#### Antifungal activity

All synthesized small molecule compounds $\mathbf{I_{1–46}}$, $\mathbf{II_{1–14}}$, and $\mathbf{III_{1–15}}$ were screened for their *in vitro* antiplant pathogenic fungi activity. Preliminary antifungal screening activities on *Rhizoctonia solani*, *Gibberella zeae*, *Bipolaris maydis, Sclerotia sclerotium*, and *Botrytis cirerea* were carried out by the plate growth rate method (31). The results were compared with the activity of a commercial agriculture fungicide,carbendazim, which was used as a positive control. Fungi were obtained from the Institute of Pesticide and Crop Protection, Sichuan University.

The tested compounds were dissolved in acetone and added to a sterile agarized Czapek–Dox medium at 45 °C. In primary screenings, compounds were used at a concentration of 200 mg/L.

The control sample contained only one equivalent of acetone. The media were poured onto 8-cm petri dishes (10 mL for each dish) and after 2 days were inoculated with 4 mm potato dextrose agar (PDA) disks of overgrown mycelium. Petri dishes were incubated at 26 °C in the dark. Two or seven days after inoculation, the diameters of the cultures were measured. The percentage inhibition of fungal growth was determined by comparison between the development of fungi colonies on media containing compounds and on the control. Three replicates of each test were carried out. Results were examined statistically using analysis of variance.

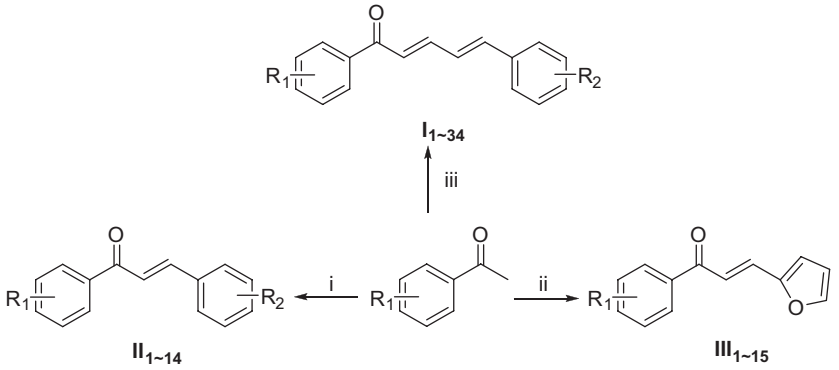
In the secondary screening, only three compounds that showed better fungal growth inhibition were used. In these experiments, the media contained five different concentrations of the compounds. Concentrations that would give 50% growth inhibition ($IC_{50}$) were calculated by linear regression between the activity and the logarithm of the concentration. Comparative studies involving carbendazim were carried out under the same conditions using solutions in acetone, and the concentrations of the fungicide were related to its active component.

## Results and Discussion

### *Synthesis of diaryl ketone building blocks*

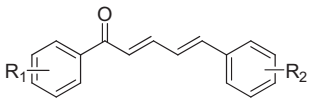
Different diaryl ketone derivatives were synthesized in alkaline solution by the Claisen–Schmidt condensation reaction as shown in Scheme 1 (32).

The optimization of the diaryl ketones as 'leitmotifs' starts in two aspects. On the one hand, diaryl was preserved, and the carbon chain was changed to change the spatial configuration and electron




**Scheme 1:** Reagents and conditions: (i) aromatic aldehyde, NaOH/EtOH, rt, 24 h; (ii) furfural, NaOH/EtOH, rt, 24 h; (iii) Cinnamaldehyde.

**Table 1:** Mortality of compound $I_{1–34}$ against *Myzus persicae* in 1000 mg/L and inhibition of compound $I_{1–34}$ for acetylcholinesterase in 50 mg/L




| No. | $R_1$ | $R_2$ | Mortality (%) | Enzyme activity (%) | No. | $R_1$ | $R_2$ | Mortality (%) | Enzyme activity (%) |
|---|---|---|---|---|---|---|---|---|---|
| **$I_1$** | H | H | 36.1 | 33.6 | **$I_{18}$** | 3,5-$F_2$ | H | 0.0 | 40.6 |
| **$I_2$** | 4-F | H | 0.0 | 39.1 | **$I_{19}$** | 3,5-$(CF_3)_2$ | H | 0.0 | 27.5 |
| **$I_3$** | 4-Cl | H | 29.4 | 36.0 | **$I_{20}$** | 4-OPh | H | 25.0 | 27.2 |
| **$I_4$** | 4-Br | H | 50.0 | 26.1 | **$I_{21}$** | 4-Ph | H | 0.0 | 42.0 |
| **$I_5$** | 4-$CH_3$ | H | 0.0 | 36.5 | **$I_{22}$** | H | 2-$NO_2$ | 0.0 | 66.4 |
| **$I_6$** | 4-$OCH_3$ | H | 25.0 | 31.2 | **$I_{23}$** | 4-F | 2-$NO_2$ | 0.0 | 96.0 |
| **$I_7$** | 4-$NO_2$ | H | 0.0 | 27.7 | **$I_{24}$** | 4-Cl | 2-$NO_2$ | 40.6 | 73.1 |
| **$I_8$** | 3-$NO_2$ | H | 34.1 | 20.5 | **$I_{25}$** | 4-Br | 2-$NO_2$ | 0.0 | 94.1 |
| **$I_9$** | 2,4-$Cl_2$ | H | 50.0 | 26.6 | **$I_{26}$** | 4-$CH_3$ | 2-$NO_2$ | 22.2 | 38.6 |
| **$I_{10}$** | 2,5-$Cl_2$ | H | 0.0 | 26.5 | **$I_{27}$** | 4-$OCH_3$ | 2-$NO_2$ | 45.8 | 88.9 |
| **$I_{11}$** | 4-F,3-$NO_2$ | H | 25.0 | 43.1 | **$I_{28}$** | 4-$NO_2$ | 2-$NO_2$ | 0.0 | 79.0 |
| **$I_{12}$** | 4-Cl,3-$NO_2$ | H | 0.0 | 39.5 | **$I_{29}$** | 3-$NO_2$ | 2-$NO_2$ | 0.0 | 69.9 |
| **$I_{13}$** | 4-Br,3-$NO_2$ | H | 30.0 | 30.4 | **$I_{30}$** | 2,4-$Cl_2$ | 2-$NO_2$ | 0.0 | 28.7 |
| **$I_{14}$** | 4-$CH_3$,3-$NO_2$ | H | 0.0 | 33.5 | **$I_{31}$** | 2,5-$Cl_2$ | 2-$NO_2$ | 25.0 | 43.1 |
| **$I_{15}$** | 4-$OCH_3$,3-$NO_2$ | H | 0.0 | 14.8 | **$I_{32}$** | 3-$CF_3$ | 2-$NO_2$ | 0.0 | 29.0 |
| **$I_{16}$** | 3-$CF_3$ | H | 33.3 | 16.8 | **$I_{33}$** | 4-OPh | 2-$NO_2$ | 0.0 | 40.6 |
| **$I_{17}$** | 4-$CF_3$ | H | 0.0 | 12.6 | **$I_{34}$** | 3,5-$F_2$ | 2-$NO_2$ | 0.0 | 77.8 |

density of the parent compounds, so compounds $\mathbf{I_{1–34}}$ were synthesized with one carbon–carbon double bond addition in comparison with the parent compounds. Meanwhile, compounds $\mathbf{II_{1–14}}$ were synthesized via the shortage of the carbon chain. On the other hand, two parent phenyls were changed, one of which was substituted by a furan ring owing to its good biologic activity; this was how compounds $\mathbf{III_{1–15}}$ were synthesized (33).

### *Evaluation of insecticidal activities and AChE inhibitory activities*

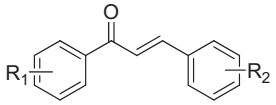
As shown in Tables 1, 2, and 3, at the concentration of 1000 mg/L, most compounds showed poor activities (mortality < 50%) against *Myzus persicae*, the mortality of some compounds was even zero. However, compound $\mathbf{II_1}$ with one fluorine atom and a three carbon atom chain showed high activity in 1000 mg/L, and its lethal rate was 72.0% against *M. persicae*. This study reveals that changes of structure cannot increase the activities of compounds against *M. persicae*.

Acetylcholinesterase inhibitory activities were measured and summarized in Tables 1, 2, and 3. At concentrations of 50 mg/L, most of the compounds showed poor inhibitory activities. Compounds $\mathbf{I_{1–34}}$, $\mathbf{I_{22}}$, $\mathbf{I_{24}}$, $\mathbf{I_{25}}$, $\mathbf{I_{27}}$, $\mathbf{I_{28}}$, $\mathbf{I_{29}}$, and $\mathbf{I_{34}}$ had better inhibitory activities (enzyme activity > 50%), and enzyme activity of compound $\mathbf{I_{25}}$ was the highest, reaching 94.1%. However, among compounds $\mathbf{II_{1–14}}$, only the enzyme activity of compound $\mathbf{II_{11}}$ was over 50% (reaching 63.4%). In line with this, among compounds $\mathbf{III_{1–15}}$, only two compounds, $\mathbf{III_3}$ and $\mathbf{III_{13}}$, showed better activities (57.3% and 87.4%). The present data show that these structure-optimized compounds have weak enzyme activity in inhibiting AChE. We have detected a similar pattern among all compounds; the increase in mortality against *M. persicae* is proportional with their ability to inhibit AChE.

### *Evaluation of antifungal activities*

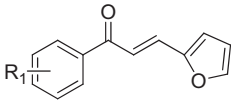
In this study, all synthesized compounds $\mathbf{I_{1–34}}$, $\mathbf{II_{1–14}}$, and $\mathbf{III_{1–15}}$ were screened for their *in vitro* antiplant pathogenic fungi activities. Their inhibition rates as antifungal agents at 200 mg/L are summarized in Table 4.

**Table 2:** Mortality of compound $II_{1–14}$ against *Myzus persicae* in 1000 mg/L and inhibition of compound $II_{1-14}$ for acetylcholinesterase in 50 mg/L




| No. | $R_1$ | $R_2$ | Mortality (%) | Enzyme activity (%) | No. | $R_1$ | $R_2$ | Mortality (%) | Enzyme activity (%) |
|---|---|---|---|---|---|---|---|---|---|
| $\mathbf{II_1}$ | 4-F | H | 72.0 | 31.2 | $\mathbf{II_8}$ | 2,4-$Cl_2$ | 4-$OCH_3$ | 0.0 | 35.8 |
| $\mathbf{II_2}$ | 4-F | 3-$NO_2$ | 0.0 | 39.6 | $\mathbf{II_9}$ | 2,4-$Cl_2$ | 3-$NO_2$ | 0.0 | 48.5 |
| $\mathbf{II_3}$ | 4-F | 4-$N(CH_3)_2$ | 0.0 | 32.0 | $\mathbf{II_{10}}$ | 2,4-$Cl_2$ | 4-$N(CH_3)_2$ | 0.0 | 26.5 |
| $\mathbf{II_4}$ | 4-F | 4-$OCH_3$, 3-$NO_2$ | 25.0 | 70.1 | $\mathbf{II_{11}}$ | 2,4-$Cl_2$ | 4-$OCH_3$, 3-$NO_2$ | 0.0 | 63.4 |
| $\mathbf{II_5}$ | 4-F | 2,4-$Cl_2$ | 0.0 | 30.4 | $\mathbf{II_{12}}$ | 4-$OCH_3$ | H | 0.0 | 20.0 |
| $\mathbf{II_6}$ | 4-F | 4-$OCH_3$ | 0.0 | 24.1 | $\mathbf{II_{13}}$ | 4-$OCH_3$ | 2,4-$Cl_2$ | 0.0 | 41.9 |
| $\mathbf{II_7}$ | 2,4-$Cl_2$ | 2,4-$Cl_2$ | 0.0 | 26.8 | $\mathbf{II_{14}}$ | 4-$OCH_3$ | 4-$OCH_3$ | 0.0 | 40.7 |

**Table 3:** Mortality of compound $III_{1-15}$ against *Myzus persicae* in 1000 mg/L and inhibition of compound $II_{1–14}$ for acetylcholinesterase in 50 mg/L




| No. | $R_1$ | Mortality (%) | Enzyme activity (%) | No. | $R_1$ | Mortality (%) | Enzyme activity (%) |
|---|---|---|---|---|---|---|---|
| $\mathbf{III_1}$ | 4-F | 54.5 | 18.8 | $\mathbf{III_9}$ | 4-Ph | 0.0 | 43.3 |
| $\mathbf{III_2}$ | 2,4-$Cl_2$ | 0.0 | 16.0 | $\mathbf{III_{10}}$ | 4-Cl,3-$NO_2$ | 0.0 | 37.5 |
| $\mathbf{III_3}$ | 4-$OCH_3$ | 25.0 | 57.3 | $\mathbf{III_{11}}$ | 4-Br,3-$NO_2$ | 0.0 | 35.8 |
| $\mathbf{III_4}$ | 4-Cl | 61.0 | 40.3 | $\mathbf{III_{12}}$ | 4-$CH_3$,3-$NO_2$ | 0.0 | 44.7 |
| $\mathbf{III_5}$ | 4-Br | 0.0 | 43.7 | $\mathbf{III_{13}}$ | 4-$OCH_3$,3-$NO_2$ | 0.0 | 87.4 |
| $\mathbf{III_6}$ | 4-$NO_2$ | 43.5 | 32.9 | $\mathbf{III_{14}}$ | 3,5-$F_2$ | 0.0 | 15.4 |
| $\mathbf{III_7}$ | 2,5-$Cl_2$ | 50.0 | 42.7 | $\mathbf{III_{15}}$ | 2-OH | 0.0 | 8.3 |
| $\mathbf{III_8}$ | 4-OPh | 0.0 | 39.7 | | | | |

**Table 4:** Antifungal activity of compounds $\mathbf{I_{1–34}}$, $\mathbf{II_{1–14}}$, and $\mathbf{III_{1–15}}$: primary screening results at concentrations of 200 mg/L

| No. | Inhibition of growth (%) | | | | |
|---|---|---|---|---|---|
| | *Rhizoctonia solani* | *Bipolaris maydis* | *Phytophthora infestans* | *Gibberella zeae* | *Sclerotia sclerotium* |
| $\mathbf{I_1}$ | 56.18 | 35.42 | 7.54 | 25.65 | 0 |
| $\mathbf{I_2}$ | 69.02 | 38.56 | 38.49 | 43.73 | 23.06 |
| $\mathbf{I_3}$ | 12.52 | 44.10 | 6.10 | 4.06 | 0 |
| $\mathbf{I_4}$ | 2.09 | 28.04 | 0 | 0 | 0 |
| $\mathbf{I_5}$ | 41.41 | 40.96 | 9.87 | 38.75 | 0 |
| $\mathbf{I_6}$ | 38.52 | 40.04 | 60.86 | 35.20 | 0 |
| $\mathbf{I_7}$ | 1.00 | 36.72 | 0 | 10.44 | 0 |
| $\mathbf{I_8}$ | 6.42 | 40.96 | 3.60 | 4.20 | 0 |
| $\mathbf{I_9}$ | 53.93 | 35.42 | 35.73 | 29.98 | 9.39 |
| $\mathbf{I_{10}}$ | 42.70 | 38.56 | 41.65 | 18.76 | 2.05 |
| $\mathbf{I_{11}}$ | 0 | 35.1 | 0 | 9.48 | 22.52 |
| $\mathbf{I_{12}}$ | 9.79 | 20.5 | 0 | 4.64 | 0 |
| $\mathbf{I_{13}}$ | 0 | 13.8 | 0 | 6.77 | 0 |
| $\mathbf{I_{14}}$ | 13.32 | 30.4 | 0 | 0 | 0 |
| $\mathbf{I_{15}}$ | 31.46 | 6.35 | 0 | 0 | 3.62 |
| $\mathbf{I_{16}}$ | 67.09 | 47.05 | 60.35 | 30.95 | 13.01 |
| $\mathbf{I_{17}}$ | 34.51 | 0 | 0 | 2.90 | 0.33 |
| $\mathbf{I_{18}}$ | 61.8 | 39.1 | 28.05 | 28.82 | 11.37 |
| $\mathbf{I_{19}}$ | 0 | 0 | 0 | 8.70 | 9.36 |
| $\mathbf{I_{20}}$ | 1.28 | 36.35 | 4.85 | 6.58 | 0 |
| $\mathbf{I_{21}}$ | 0 | 0 | 0 | 0 | 24.85 |
| $\mathbf{I_{22}}$ | 8.9 | 0 | 8.5 | 0 | 0 |
| $\mathbf{I_{23}}$ | 6.3 | 9.3 | 7.0 | 9.2 | 7.3 |
| $\mathbf{I_{24}}$ | 5.3 | 7.6 | 0 | 0 | 0 |
| $\mathbf{I_{25}}$ | 3.0 | 0 | 4.0 | 8.2 | 15.3 |
| $\mathbf{I_{26}}$ | 6.3 | 12.3 | 15.1 | 0 | 12.0 |
| $\mathbf{I_{27}}$ | 10.3 | 0 | 2.0 | 0 | 6.3 |
| $\mathbf{I_{28}}$ | 0 | 8.8 | 7.0 | 12.0 | 7.6 |
| $\mathbf{I_{29}}$ | 0 | 0 | 3.3 | 3.0 | 0 |
| $\mathbf{I_{30}}$ | 14.3 | 9.9 | 6.28 | 7.0 | 6.2 |
| $\mathbf{I_{31}}$ | 0 | 0 | 0 | 5.3 | 16.8 |
| $\mathbf{I_{32}}$ | 20.5 | 8.79 | 0 | 15.1 | 1.02 |
| $\mathbf{I_{33}}$ | 18.3 | 0 | 3.3 | 6.37 | 2.3 |
| $\mathbf{I_{34}}$ | 0 | 0 | 30.6 | 6.5 | 0 |
| $\mathbf{II_1}$ | 45.26 | 49.14 | 86.93 | 56.44 | 32.82 |
| $\mathbf{II_2}$ | 20.47 | 21.21 | 0 | 13.86 | 0 |
| $\mathbf{II_3}$ | 57.40 | 40.0 | 62.67 | 21.78 | 2.29 |
| $\mathbf{II_4}$ | 26.00 | 15.0 | 0 | 15.25 | 0 |
| $\mathbf{II_5}$ | 50.62 | 30.17 | 0 | 22.18 | 0 |
| $\mathbf{II_6}$ | 60.30 | 37.07 | 70.75 | 26.73 | 7.33 |
| $\mathbf{II_7}$ | 47.86 | 18.62 | 0 | 21.19 | 0 |
| $\mathbf{II_8}$ | 75.13 | 46.03 | 0 | 33.67 | 48.55 |
| $\mathbf{II_9}$ | 15.35 | 12.07 | 0 | 23.76 | 0 |
| $\mathbf{II_{10}}$ | 55.46 | 18.62 | 0 | 29.70 | 40.0 |
| $\mathbf{II_{11}}$ | 6.64 | 0 | 0 | 17.23 | 0 |
| $\mathbf{II_{12}}$ | 60.17 | 48.28 | 46.50 | 25.74 | 24.73 |
| $\mathbf{II_{13}}$ | 11.76 | 20.17 | 0 | 21.78 | 7.33 |
| $\mathbf{II_{14}}$ | 66.39 | 46.21 | 70.35 | 43.96 | 28.24 |
| $\mathbf{III_1}$ | 100 | 81.03 | 90.50 | 83.17 | 80.15 |
| $\mathbf{III_2}$ | 100 | 77.59 | 3.0 | 69.31 | 74.35 |
| $\mathbf{III_3}$ | 100 | 78.97 | 73.61 | 54.85 | 83.51 |
| $\mathbf{III_4}$ | 91.74 | 59.62 | 5.01 | 55.82 | 7.46 |
| $\mathbf{III_5}$ | 81.68 | 56.01 | 0 | 54.10 | 2.69 |
| $\mathbf{III_6}$ | 11.43 | 52.58 | 0 | 4.50 | 1.94 |
| $\mathbf{III_7}$ | 88.43 | 80.54 | 0 | 64.42 | 54.18 |
| $\mathbf{III_8}$ | 73.42 | 40.72 | 6.72 | 17.06 | 21.94 |
| $\mathbf{III_9}$ | 66.39 | 10.62 | 10.34 | 14.15 | 22.39 |
| $\mathbf{III_{10}}$ | 1.79 | 29.92 | 0 | 4.10 | 1.45 |
| $\mathbf{III_{11}}$ | 0 | 38.66 | 8.23 | 9.92 | 2.23 |
| $\mathbf{III_{12}}$ | 44.35 | 28.03 | 21.03 | 11.38 | 6.54 |
| $\mathbf{III_{13}}$ | 7.02 | 31.44 | 0 | 1.00 | 15.67 |
| $\mathbf{III_{14}}$ | 82.23 | 57.53 | 80.64 | 49.47 | 44.03 |
| $\mathbf{III_{15}}$ | 88.43 | 26.36 | 30.14 | 37.83 | 38.51 |

**Table 5:** $IC_{50}$ values (mg/L) of selected compound $\mathbf{III_{1–3}}$

| No. | *Rhizoctonia solani* | *Bipolaris maydis* | *Gibberella zeae* | *Sclerotia sclerotium* |
|---|---|---|---|---|
| $\mathbf{III_1}$ | 7.72 | 22.66 | 45.13 | 43.14 |
| $\mathbf{III_2}$ | 1.20 | 29.49 | 104.89 | 37.84 |
| $\mathbf{III_3}$ | 4.02 | 38.88 | 42.03 | 45.77 |
| Carbendazim | 4.36 | 0.76 | 1.02 | 0.89 |

$IC_{50}$ values are defined as inhibitory concentration at which there is a half growth.

In our initial experimental design, compounds $\mathbf{I_{1–34}}$ were synthesized based on the fact that the carbon–carbon double bond addition changed the spatial configuration and electron density of the parent compounds, thus increasing their biologic activities. However, as shown in Table 1, these compounds showed poor abilities against *M. persicae*. Their abilities against pathogenic fungi were then examined in this study.

As shown in Table 4, the *in vitro* bioassay showed that most compounds exhibited poor activities against all six fungi at concentrations of 200 mg/L. However, compounds $\mathbf{I_1}$, $\mathbf{I_2}$, $\mathbf{I_9}$, $\mathbf{I_{16}}$, and $\mathbf{I_{18}}$ exhibited good activities against *R. solani*, and compound $\mathbf{I_6}$ showed the best performance against *Phytophthora infestans*. This structure-oriented increase in antifungal activity urged us to examine another group of synthesized products ($\mathbf{II_{1–14}}$) where the substituent groups remained the same but the carbon chains were altered.

Compounds $\mathbf{II_{1–14}}$ showed better antifungal activities in comparison with the compounds $\mathbf{I_{1–34}}$. This observance supported our hypothesis that a carbon–carbon double bond change may affect biologic activities. Data S1 also came from another group of compounds ($\mathbf{III_{1–3}}$) where one furan ring replaced one parental phenyl structure. These three compounds showed strong antifungal activities (all reaching 100%) against *R. solani* at concentrations of 200 mg/L. In addition, the three compounds also showed better activities against other plant pathogenic fungi in comparison with compounds $\mathbf{II_{1–14}}$.

The strong antifungal activities of compounds $\mathbf{III_{1–3}}$ revealed the importance of the furan ring for antifungal activity enhancement. To keep the furan ring, compounds $\mathbf{III_{4–15}}$ had been synthesized where the other phenyl ring had been further modified (Scheme 1). As shown in Table 4, compounds $\mathbf{III_{4–15}}$, which had strong activities, revealed the importance of the furan ring in antifungal activities.

Compared with the antifungal activities of compounds **$III_1$**, **$III_2$**, and **$III_3$**, the activities of compounds **$III_{4–15}$** were lower. This also confirmed for us that one compound with substituent groups –F, –$OCH_3$, and –Cl on the phenyl ring possessed higher antifungal activities than the other compounds with the other groups, such as –$NO_2$, –Br, and –Ph.

As shown in Table 4, in comparison with compounds **$III_{4–15}$**, compounds **$III_{1–3}$** showed strong activities against a much wider spectrum of fungi. In this study, their abilities against fungi were further examined. As shown in Table 5, compound **$III_2$** and compound **$III_3$** showed strong activities against *R. solani* ($IC_{50}$ = 1.20 mg/L for **$III_2$** and $IC_{50}$ = 4.02 mg/L for **$III_3$**). In comparison with the commercial agriculture fungicide carbendazim ($IC_{50}$ = 4.36 mg/L), these two compounds show strong potential as a commercial fungicide.

## Conclusion

In conclusion, we have synthesized three series of compounds with a diaryl ketone moiety as pharmacophores. Preliminary bioassays and biochemical analyses showed that compounds **$I_{1–46}$**, **$II_{1–14}$**, and **$III_{1–15}$** possessed weak insecticidal activities and AChE inhibitory activities. However, we found that compound **III** with a furan ring had strong antifungal activities. Among the examined compounds, the $IC_{50}$ of compound (***E***)**-1-(2,4-dichlorophenyl)-3-(furan-2-yl)prop-2-en-1-one (**$III_2$**)** was 1.20 mg/L against *R. solani* suggesting its strong potential as a novel antifungal drug. To our knowledge, this was the first comprehensive report about antifungal drug screenings based on natural products from *S. chamaejasme* L. Further structural modifications and antifungal activities optimization on these analogs will be conducted.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Appendix S1.** Characterization of all products by 1H NMR.

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