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Synthesis and biological activities of (*E*)-β-farnesene analogues containing 1,2,3-thiadiazole

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ABSTRACT

In order to discover novel compounds with high-activity to control aphid, a series of novel (*E*)-β-farnesene analogues containing 1,2,3-thiadiazole were designed and synthesized, and their structures were confirmed by IR, ^{1}H NMR, ^{13}C NMR, and HRMS (ESI). The stability of representative compounds was studied by HPLC and ^{1}H NMR techniques. Repellent activity results indicated that compounds **8h** and **8j** displayed 60.3% and 62.0% repellent rates, respectively. The aphicidal bioassay results showed that most analogues exhibited considerable aphicidal activity against *Myzus persicae*. Especially, analogues **8l**, **8s** and **8t** exhibited high activity with LC_{50} values of 33.4 μg/mL, 50.2 μg/mL and 61.8 μg/mL, respectively, which were higher than the lead compound (*E*)-β-farnesene, but lower than commercial insecticide pymetrozine with a LC_{50} of 7.1 μg/mL.

1. Introduction

Aphids are important agricultural pests throughout the world, often causing major economic losses. Their abilities of fast breeding and easily developing resistance to insecticides make their population control challenging [1]. Recently, the eco-toxicity of some neonicotinoid insecticides to bees has led to call for restrictions on their use in agriculture [2]. Therefore, it becomes necessary to find eco-friendly chemicals with new strategy. The major component of aphid alarm pheromone, (*E*)-β-farnesene (Eβf, Fig. 1), is released when aphids are attacked by natural enemies and is also repellent to other aphids, causing avoidance behaviour when detected [3–6]. Moreover, its insecticidal activity at high doses has also been demonstrated [7]. Parasitoid and predators, on the other hand, eavesdrop on aphid communication and utilize Eβf as a kairomone, which attracts aphid predators and enhances foraging behaviour of parasitoids [8,9]. Therefore, it is a potentially valuable tool in the development of new aphid control strategies. However, field application of this pheromone presents some disadvantages for its relative volatility and instability in the environment caused by easy oxidation of its conjugated double bonds [10]. Therefore, it is necessary to find new Eβf analogues that are more stable and efficient.

As an important class of nitrogen-containing compounds, 1,2,3-thiadiazole with various interesting properties is becoming a rapidly growing and independent branch of the heterocyclic chemistry [11]. It is widely used in chemicals discovery, and has increasingly aroused attention because of its versatile biological activities, such as insecticidal, systemic acquired resistance, fungicidal, herbicidal and antiviral activities [12–19]. Recently, a large number of 1,2,3-thiadiazole derivatives were found to exhibit insecticidal activities. For example, Fan found that a series of 1,2,3-thiadiazole derivatives containing diacylhydrazine moiety possessed superior insecticidal activities against *Plutella xylostella* L. and *Culex pipiens pallens* [20]. More significantly, the structure of 1,2,3-thiadiazole can be easily decomposed into lower molecular weight compounds by releasing N_2, which favours the use of its derivatives as eco-friendly pesticides with low toxicity and suitable duration of efficiency to the target biology and half-life in the agroecosystem [11].

In our previous studies, some Eβf analogues with good stability and biological activity were obtained by introducing a variety of aromatic ring skeleton to replace the conjugated double bonds in Eβf [1,21,22]. These studies inspired our current hypothesis that the introduction of 1,2,3-thiadizole moiety into the lead compound Eβf may favour the biological activity of Eβf. Here we designed and

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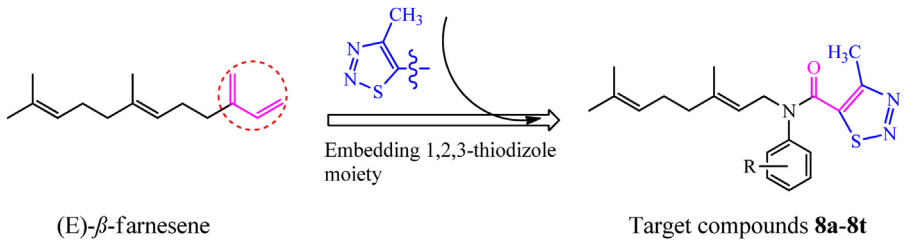


Fig. 1. Design strategy of the target compounds.

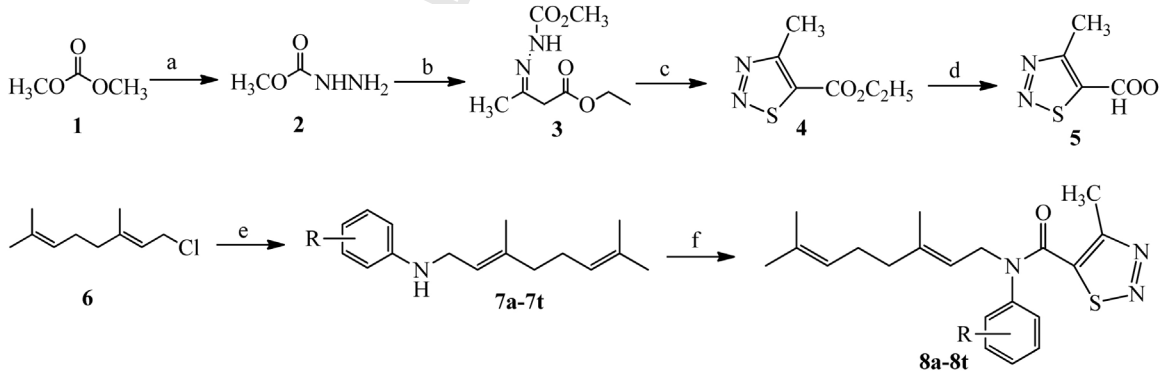
synthesized a series of Eβf analogues containing 1,2,3-thiadiazole (Fig. 1) thanks to its superior properties as described above. Accordingly, the designed compounds contain the geranyl group, mimicking the terpene structure of Eβf, linked to 1,2,3-thiadizole ring. Especially, the conjugated double bonds of Eβf are part of the aromatic ring in the analogues. The good stability and biological activities of these Eβf analogues were expected. The stability of representative compounds was studied by HPLC and ^{1}H NMR technologies. Their aphicidal and repellent activities against *Myzus persicae* (Sulzer) were evaluated. It is expected that this study may be valuable for the discovery of eco-friendly aphid control agents.

2. Results and discussion

2.1. Chemistry

The synthetic route for the title compounds **8a–8t** was illustrated in Scheme 1. First, the key intermediate 4-methyl-1,2,3-thiadiazole-5-carboxylic acid **5** was synthesized from dimethyl carbonate through four steps: Hydrazidation, condensation, cyclization, and saponification with the total yield 68.2%. Second, the synthetic method of compounds **7a–7t** have been reported in Ref. [22], when geranyl chloride as alkylating agents reacted with aniline only in the present of K_2CO_3, the reaction proceeded slowly and dialkylation by-products are observed. In order to improve the selectivity and reaction yield, we choose one optimized reaction condition: 3 equiv of aniline and a catalytic amount of KI (0.1 equiv) in acetonitrile, additional 1 equiv K_2CO_3 and 3 equiv *N*,*N*-dimethyldodecylamine-*N*-oxide (DDAO), at room temperature for 4 h. And we successfully obtained **7b–7t** in this condition through the reaction of geranyl chloride with different substituted aniline in the yields of 39–83%. Finally, the target compounds were readily obtained in 34–92% yields through the condensation reaction between compound **5** and compounds **7a–7t** at room temperature in the presence of the condensation reagent *N*,*N*′-dicyclohexyl-carbodiimide (DCC) and the promoter 4-dimethy-lamino-pryidine (DMAP).

The structures of the synthesized compounds (**8a–8t**) were established on the basis of their spectroscopic data of NMR, IR and HRMS (Supporting information). As indicated by ^{1}H NMR, all aryl protons showed multiplets at δ 6.78 to δ 8.20, and the positions of the two double bonds' protons were showed multiplet at δ 4.91 to δ 5.02 and triplet at about δ 5.26 respectively. Signals corresponding to the $-CH_3$ of the 1,2,3-thiadiazole ring were observed at about δ 2.82 and signals for the C–CH_2–CH_2–C protons were observed at δ 1.92 to δ 2.05. Three $-CH_3$ absorption peaks showed singlet at about δ 1.48, δ 1.59 and δ 1.68, respectively. Interestingly, the signal of CH_2–N protons is change along with the substituent in different position of phenyl. Normally, this absorption peak is a doublet at about δ 4.46 with coupling constants 7.20 Hz. However, when the substituent is at the ortho of phenyl ring, the signal will split two quartets in average (Supporting information). We considered that this phenomenon is from the existing steric hindrance of R at the *ortho* position. Therefore, the conformational switching of corresponding compound is slowly at room temperature (low energy), and this led to the compound not existed with only one preferential conformation. In order to verify this deduction, we further chose compound **8n** (R = 2-OCH_3) as example to study by dynamic ^{1}H NMR spectroscopy. As a result, the 'abnormal split' of the signal of CH_2–N protons was vanish and replaced with a singlet at δ 4.37 in the 100 °C ^{1}H NMR spectrum (Supporting information). This result is identical with our guess, in which the conformational switching of compound **8n** is quickly at high temperature (high energy).



Scheme 1. Synthetic route of the designed compounds. Reagents and conditions: (a) hydrazine hydrate, ethanol, r.t. 24 h; (b) ethyl acetoacetate, ethanol, r.t. 10 h; (c) $SOCl_2$, CH_2Cl_2, 0 °C–r.t. 24 h; (d) CH_3OH/NaOH, HCl/H_2O, r.t. 12 h; (e) substituted anilines, K_2CO_3, KI, DDAO, CH_3CN, r.t. 4 h; (f) 4-methy-1,2,3-thiadizole-5-carboxylic acid **5**, DCC, DMAP, CH_2Cl_2, r.t. 6–10 h.

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Table 1
Stability data of representative compounds.

Compd.	Content/% (0 h)	Content/% (48 h)	Compd.	Content/% (0 h)	Content/% (48 h)
8a	100.00	100.00	**8l**	98.18	97.99
8b	98.42	98.45	**8n**	98.88	98.80
8g	99.08	98.51	**8q**	99.66	99.48
8h	100.00	100.00	**8s**	99.14	99.06

These compounds were found to be stable at room temperature. In particular, we checked the contents change of eight compounds by HPLC technique, and these data were shown in Table 1. The Eβf is easy oxidation because of its conjugated double bonds, and it degrades 77% and 94% after exposure to air for 24 h and 45 h at room temperature, respectively [23]. We have found the accordant result in our previous study that Eβf was decomposed absolutely after leaving it at room temperature and in contact with air for periods up to 48 h [21]. As indicated in Table 1, in such conditions the degradation of the candidate compounds could not be detected. Moreover, we took ^{1}H NMR technique to study the protons change of compound **8a**, and Fig. 2 illustrated the ^{1}H NMR spectrums of compound **8a** after exposure to air for 1 day, 3 days, 5 days and 7 days. As a result, there was neither proton signals disappeared nor new proton signals appeared. On the basis of the above results, the stability of the title compounds is much better than that of the lead compound Eβf.

2.2. Biological activity

The repellent effects of analogues on *M. persicae* were evaluated and listed in Table 2. The results indicated that except for **8n**, compounds **8a**–**8t** displayed certain repellent activities against *M. persicae* at 5 μg dose. Some of them displayed promising repellent effect with values of 18.7–62.0%. Particularly, compounds **8h** and **8j** showed 60.3% and 62.0% repellent rates, respectively. Repellent activities of target compounds were affected by both variation of the substitute's type and position on the phenyl. When the substituent R was at *para* position of phenyl, compounds with weak electron-withdrawing groups (such as 4-F, 4-Br) were more effective than those with electron-donating groups (such as 4-CH_3, 4-OCH_3). Additionally, compounds with di-substituents on the phenyl showed lower effectiveness than those with mono-substituent. For example, the repellent rate of compound **8h** (with a 2-F substituent) was much higher than those of **8r** (with a 2,6-F_2 substituent) and **8s** (with a 2,4-F_2 substituent). Furthermore, the position of the substituent R on the phenyl interestingly affected the repellent activity. Amongst the analogues containing a halogen substituent, the order of the repellent activities of compounds **8k** (2-Br), **8l** (3-Br), and **8m** (4-Br) could be placed as following: **8m** > **8k** > **8l**. Also, compounds **8e**, **8f**, **8g**, and **8h**, **8i**, **8j**, had the similar results. However, the analogues with electron-donating groups on the benzene ring exhibited another rule, for instance, the repellent activities of compounds **8n** (2-OCH_3), **8o** (3-OCH_3), and **8p** (4-OCH_3) could be found as following: **8p** > **8o** > **8n**.

The aphicidal activity of the lead compound, the target compounds, and pymetrozine against *M. persicae* was shown in Table 3. The preliminary bioassay results (at a concentration of 200 μg/mL, 48 h) indicated that all the target compounds exhibited aphicidal activity. The aphicidal activities of analogues **8d**, **8e**, **8f**, **8h**, **8j**, **8l**, **8o**, **8p**, **8r**, **8s**, and **8t** are comparable to or even better than that of the lead compound Eβf. Unluckily, the aphicidal activities of all the compounds are weaker than that of pymetrozine. On the basis of the primary experimental results, analogues showing a mortality rate higher than 70% were chosen to determine the LC_{50} values. As shown in Table 4, compounds **8l**, **8s**, and **8t** exhibited high aphicidal activity against *M. persicae* with LC_{50} values of 33.4, 50.2 and 61.8 μg/mL, respectively. However,

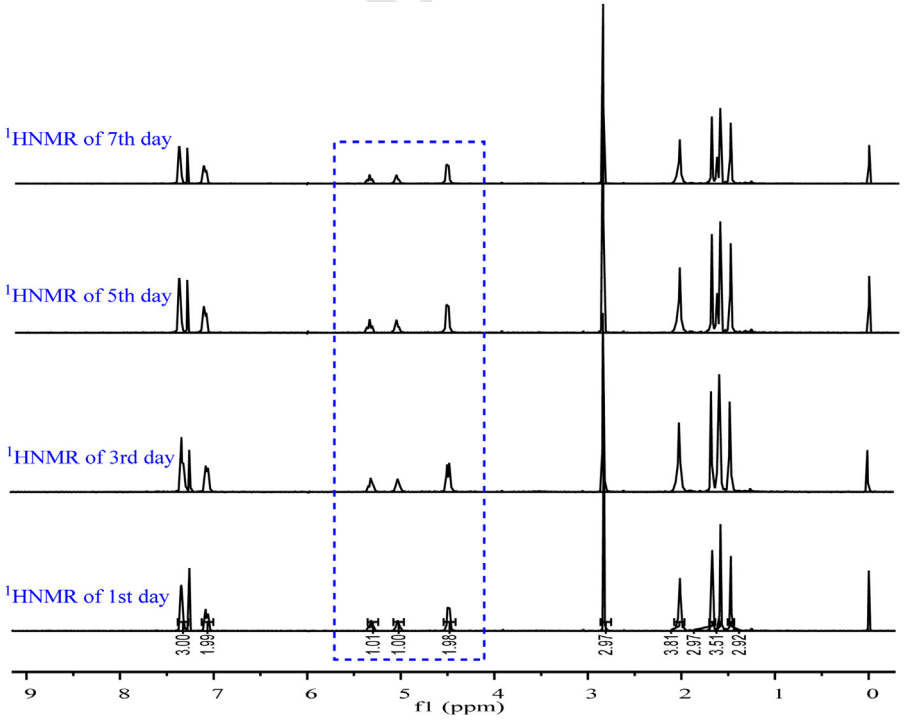

Fig. 2. The ^{1}H NMR spectrums of compound **8a**.

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Table 2
The repellent activities of title compounds **8a–8t** (5 μg/test, *Myzus persicae*).

Compd.	R	Repellent rate (%)[a]	Compd.	R	Repellent rate (%)
8a	H	55.6 ± 5.9	**8k**	2-Br	51.8 ± 5.5
8b	2-CH_3	31.2 ± 4.9	**8l**	3-Br	33.2 ± 4.6
8c	3-CH_3	34.7 ± 1.9	**8m**	4-Br	59.0 ± 3.0
8d	4-CH_3	42.5 ± 5.0	**8n**	2-OCH_3	0.0
8e	2-Cl	50.8 ± 6.4	**8o**	3-OCH_3	18.7 ± 4.2
8f	3-Cl	39.1 ± 4.2	**8p**	4-OCH_3	49.3 ± 2.5
8g	4-Cl	58.2 ± 2.4	**8q**	4-NO_2	36.6 ± 2.3
8h	2-F	60.3 ± 2.3	**8r**	2,6-F_2	21.9 ± 2.8
8i	3-F	43.4 ± 0.7	**8s**	2,4-F_2	24.5 ± 3.0
8j	4-F	62.0 ± 1.4	**8t**	3-Cl-4-CH_3	32.7 ± 3.6
Eβf[b]	–	87.4 ± 2.3			

[a] Average of three replicates.
[b] Eβf was used as a positive control.

Table 3
The aphicidal activity against *Myzus persicae* of title compounds **8a–8t** (200 μg/mL, 48 h).

Compd.	R	Screening mortality (%)[a]	Compd.	R	Screening mortality (%)
8a	H	44.9 ± 6.6	**8l**	3-Br	73.3 ± 8.5
8b	2-CH_3	38.4 ± 6.8	**8 m**	4-Br	57.4 ± 9.0
8c	3-CH_3	34.3 ± 3.7	**8n**	2-OCH_3	54.4 ± 5.4
8d	4-CH_3	59.7 ± 5.6	**8o**	3-OCH_3	58.0 ± 6.2
8e	2-Cl	59.5 ± 7.4	**8p**	4-OCH_3	61.9 ± 9.1
8f	3-Cl	65.2 ± 6.8	**8q**	4-NO_2	45.1 ± 8.3
8g	4-Cl	50.3 ± 7.9	**8r**	2,6-F_2	71.2 ± 5.1
8h	2-F	69.1 ± 5.7	**8s**	2,4-F_2	67.1 ± 8.3
8i	3-F	52.8 ± 2.7	**8t**	3-Cl-4-CH_3	72.6 ± 3.6
8j	4-F	60.4 ± 3.6	Eβf	–	58.8 ± 2.9
8k	2-Br	36.4 ± 4.5	Pymetrozine[b]	–	87.1 ± 2.1

[a] Average of three replicates.
[b] Pymetrozine was used as a positive control.

Table 4
The LC_{50} of compounds **8l**, **8r** and **8t**.

Compd.	LC_{50} (95% FL), μg/mL	Toxic regression equation	R
8l	33.4 (20.6–53.5)	$y = 1.619x - 2.467$	0.958
8r	50.2 (30.4–84.5)	$y = 1.465x - 2.492$	0.983
8t	61.8 (37.9–103.5)	$y = 1.465x - 2.492$	0.918
Pymetrozine	7.1 (4.3–10.7)	$y = 1.770x - 1.502$	0.950

the aphicidal activities of analogues **8l**, **8s**, and **8t** are lower than pymetrozine with a LC_{50} of 7.1 μg/mL.

3. Conclusion

In summary, a series of novel (*E*)-*β*-farnesene analogues containing 1,2,3-thiadiazole were designed and synthesized by replacing unstable conjugated double bonds of Eβf with1,2,3-thiadiazole ring according to the principle of linking bioactive substructures. The stability of representative compounds is much better than the lead Eβf based on the results made by HPLC and ^{1}H NMR techniques. Behaviour experiment results indicated that compounds **8h** and **8j** displayed 60.3% and 62.0% repellent rate, respectively. Interestingly, compounds with weak electron-withdrawing groups (such as 4-F, 4-Br) were more effective than those with electron-donating groups (such as 4-CH_3, 4-OCH_3) when the substituent is at para position of phenyl. The aphicidal bioassay results showed that most analogues exhibited considerable aphicidal activity against *M. persicae*, especially analogues **8l**, **8s** and **8t** exhibited high aphicidal activity against *M. persicae* with LC_{50} values of 33.4, 50.2 and 61.8 μg/mL, respectively, which exhibited improved aphicidal activity compared with the lead Eβf. This work could afford some valuable information on the discovery of eco-friendly aphid control agent.

4. Experimental

4.1. Synthesis

Melting points of some compounds were determined on an X-4 binocular microscope (Fukai Instrument Co., Beijing, China), with an uncorrected thermometer. ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on Bruker AM-300 (300 MHz, 75 MHz respectively) spectrometer with $CDCl_3$ as the solvent and TMS as the internal standard. High resolution mass spectrometry (HRMS) data were obtained on an FTICR-MS Varian 7.0 T FTICR-MS instrument. Purity was analysed by high performance liquid chromatography (HPLC) on a LC-1AT HPLC instrument (Shimadzu). All the reagents were obtained commercially and used after further purification. Column chromatography purification was carried out by using silica gel (Merck 60, 200–300 mesh).

The general synthetic scheme for representative compounds **8a–8t** is shown in Scheme 1. Key intermediate **5** was prepared from dimethyl carbonate according to Ref. [12]. Compounds **7a–7t** were obtained through N-alkylation reaction between geranyl chloride and different substituted aniline according to the reported method [22,24–26]. The general procedures of **5** and **7a–7t** are described in the Supporting information.

The target compounds **8a–8t** were prepared using condensation reaction between compounds **5** and **7a–7t**. The general procedure was described as below. To a solution of **5** (0.87 g, 6 mmol), DMAP (0.15 g, 1.2 mmol) and dichloromethane (20 mL), DCC (1.36 g, 6.6 mmol) was added in batches. And then solution of compounds **7a–7t** (6.0 mmol) in dichloromethane was dropped slowly, the resulted mixture was stirred for 6–10 h. After the reaction completed, filtered, the filtrate was washed with water. The organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Then the residue was purified by

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chromatography on silica-gel column (petroleum ether:ethyl acetate = 15:1, v/v) to obtain the corresponding analogues **8a**–**8t**.

4.2. Stability test

The representative analogues **8a** (H), **8b** (2-CH_3), **8g** (4-Cl), **8h** (2-F), **8l** (3-Br), **8n** (2-OCH_3), **8q** (4-NO_2) and **8s** (2,4-F_2) were dissolved in methanol (chromatographically pure), respectively. After exposure to air for 48 h at room temperature, their changes of content were analysed by high performance liquid chromatography (HPLC) on a LC-1AT HPLC instrument (Shimadzu). Chromatographic experiments were performed on C18 reversed-phase column (4.5 mm × 250 mm, 5 μm), the mobile phase was methanol and water (85:15); the detection wavelength was 254 nm, column temperature was 25 °C, the flow rate was 0.7 mL/min and the injection volume was 5 μL.

Meanwhile, the compound **8a** was selected to study its stability by ^{1}H NMR technology. Dissolved in $CDCl_3$, **8a** was tested 4 times at corresponding time successively after exposure to air for 1 day, 3 days, 5 days, 7 days at room temperature, the changes of proton were analysed by ^{1}H NMR spectrograms.

4.3. Bioassays

The behavioural activity and aphicidal assay against *M. persicae* was evaluated according to the reference methods [27–31]. In the repellent assay, in each test 5 μg compound (2.5 μL of hexane solution of each compound with a concentration of 2000 μg/mL) was placed in the glass stimulus chamber of the "treatment" arm. As a control, 2.5 μL of hexane was placed in the glass stimulus chamber of the "control" arm of the olfactometer. The detailed procedures were listed in the Supporting information.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.cclet.2016.10.030.

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