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Larvicidal Activity of Geranylacetone Derivatives against *Culex quinquefasciatus* Larvae and Investigation of Environmental Toxicity and Non-Target Aquatic Species

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Abstract: A grindstone method based on Mannich condensation was used to synthesize geranylacetone derivatives (**1a–1f**). The method showed a high yield under milder reaction conditions. Analyses of the synthesized compounds were carried out by FTIR, ^{1}H, ^{13}C NMR, mass spectrometry, and elemental analysis. We synthesized and evaluated the larvicidal and ichthyotoxic activities of six compounds (**1a–1f**) in this study. Compound **1f** (5,9-dimethyl-1-phenyl-3-(2-(3-phenylallylidene)hydrazinyl)deca-4,8-dien-1-one) was more active (LD_{50}: 14.1 µg/mL) against the second instar larvae of *Culex quinquefasciatus* than geranylacetone (67.2 µg/mL), whereas the former caused 13.9% mortality at 100 µg/mL. Geranylacetone, in an antifeedant screening test, showed 53.1% against *Oreochromis mossambicus* within 24 h. The compound **1f** showed high larvicidal activity against *C. quinquefasciatus* and was non-toxic to non-target aquatic species.

Keywords: Mannich base; geranylacetone; grindstone chemistry; Green Chemistry approach; larvicidal activity; *Culex quinquefasciatus*; ichthyotoxicity

1. Introduction

Mosquitoes are important vectors of several diseases, including malaria [1,2]. In several regions, *Culex quinquefasciatus* is associated with several vector-borne diseases. Insecticides designed to kill larvae are called larvicides. As an insect growth controller, metaprene prevents the larvae from returning to the pupa stage significantly after their growth period has been interrupted [3]. The pesticide methoprene is mildly toxic to crabs, shrimp, lobster, and crayfish, as well as to fish and aquatic herbivores; in fact, it tends to accumulate in the tissues of fishes. Toxins produced by fishes or compounds toxic to them are ichthyotoxins [4]. The euglenophyceae and prymnesium, made by algae can cause large-scale fish deaths [5]. Toxin-producing algae are found both in freshwater and marine environments. It is important to keep in mind that the severity of ichthyotoxic poisoning (in humans) varies depending on how much of the toxin was consumed. An ichthyotoxin poisoning can result in headaches, diarrhea, dizziness, high blood pressure, and other symptoms [6].

The Literature survey based on geranylacetone natural products and relative compounds, reveals that 9-geranylnyl-p-cymene is a rare diterpene originally observed in Helichrysum species, also members of the Asteraceae family (Figure 1) [7,8].

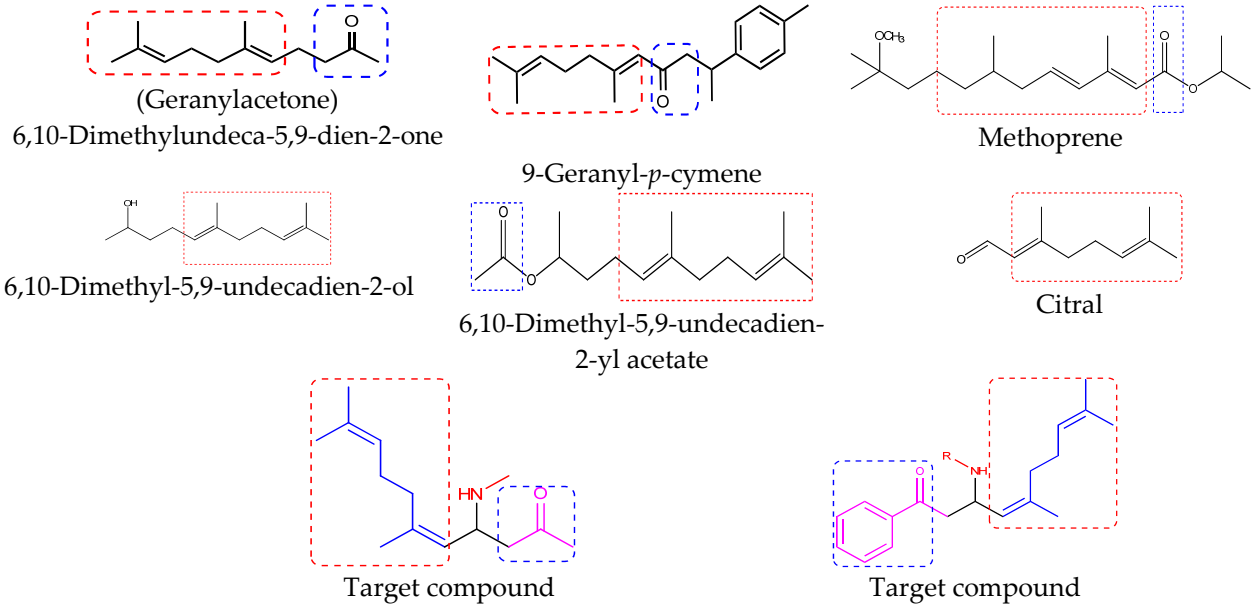


Figure 1. Undeca-5,9-dien-1-one (Geranylacetone derivatives).

9-(15,16-Dihydro-15-methylene)-geranyl-*p*-cymene and 9-(15,16-dihydro-15-methylene)-geranyl-α-terpinene were first identified in the essential oils of the flowers of *Tanacetum annuum* (Asteraceae) [9,10]. Larvicidal activity of *Eucalyptus globulus* leaf essential oil was effective against 4th instar larvae of *C. quinquefasciatus* compared to Temephos [11]. Geranylacetone (GA) is a flavor component of many plants including rice, mango, and tomatoes [12]. In addition, b-cyclocitral, b-ionone, and geranylacetone are known insect repellants. Together with other ketones, geranylacetone results from the degradation of vegetable matter by ozone [13]. Geranylacetone is a monoterpene ketone that contains a geranyl group fused to α-methyl of acetone. Geranylacetone was isolated from Keetia leucantha + (K. Krause), and Bridson (Rubiaceae) [14]. Figure 1 shows active geranylacetone, sulcatone, fuscumol, fuscumol acetate, and (sulcatol).

In the food industry and medicine, GA is a white or yellowish oily liquid at room temperature that dissolves slowly in water and is volatile. Its application in these fields is limited. GA's water solubility and stability need to be improved in order for its application to expand [15]. The researchers studied the slow-release adsorption and adsorption effects of GA on various adsorption materials, and the improved GA stability. It has also been demonstrated that geranylacetone is an antimicrobial compound when examined as a food preservative. Chemicals are used as insecticides against vector mosquitoes [16], although their usage is limited because of their toxic effects on the environment and other organisms [17,18]. Various larvicidal active targets were published in previous years, but chemical insecticides pose a bigger risk with numerous potential environmental problems, including widespread development of resistance and disruption of natural biological control processes [19,20]. In order to overcome the challenges and limitations described above, we developed a grindstone chemistry methodology which we applied to the synthesis of novel geranylacetone derivatives and examined their larvicidal activity.

2. Materials and Method

All compounds were analyzed with a Nicolet iS5 FTIR (4000–400 cm^{-1}) by Thermo Scientific. Spectra for ^{1}H and ^{13}C were analyzed using the Bruker DRX-300 MHz. We analyzed (C, H, N, and S) elements and their percentages (%) using an elemental analyzer (model Vario EL III). Perkin Elmer GCMS model Clarus SQ8 (EI) was used to record mass spectra.

2.1. Synthesis of Compound **1a–f***: General Procedure*

A reaction mixture of cinnamaldehyde (0.01 mole), acetone (or) acetophenone (0.01 mole), substituted amine (0.01 mole) was mixed and ground at room temperature. Separation of the solid material was performed using column chromatography (Ethyl acetate 4: hexane 6). The same method was followed when mixing compounds **1b**–**1f**.

2.1.1. 6,10-Dimethyl-4-(2-phenylhydrazinyl)undeca-5,9-dien-2-one (**1a**)

Yield 87%; mw: 300.44; mp: 175 °C; IR (cm^{-1}): 3356, 3172, 2726, 1627; ^{1}H NMR (300 MHz): δ 7.37 (t, 2H, *J* = 6.23 Hz), 7.06 (d, 2H, *J* = 6.21 Hz), 6.90 (t, 1H, *J* = 6.23 Hz), 5.33 (1H, s), 5.20 (s, 2H), 3.58(s, 1H), 2.88 (s, 1H), 2.79 (d, 2H, *J* = 6.21Hz), 2.31 (d, 2H, *J* = 6.21 Hz), 2.00 (m, 4H), 2.13 (s, 3H), 1.82 (s, 6H), 1.70 (s, 3H); ^{13}C NMR (300 MHz): 207.7, 135.1, 132.0, 127.7, 123.5, 123.4, 151.0, 129.2, 122.8, 133.2, 53.5, 49.7, 47.6, 39.7, 31.0, 26.4, 29.8, 24.6, 18.6, 16.4; EI-MS (m/z): 300.22 (M^+,22%); Elemental analysis: Calcd. For ($C_{19}H_{28}N_2O$): C, 75.96; H, 9.39; N, 9.32%; Found: C, 75.97; H, 9.34; N, 9.30%.

2.1.2. 5,9-Dimethyl-1-phenyl-3-(phenylamino)deca-4,8-dien-1-one (**1b**)

Yield 89%; mw: 347.49; mp: 169 °C; IR(cm^{-1}): 3352, 3168, 2722, 1623; ^{1}H NMR (300 MHz): δ 9.40 (s, 1H), 8.18 (s, 1H), 7.37 (t, 2H, *J* = 6.23 Hz), 7.53 (t, 2H, *J* = 6.23 Hz), 7.63 (t, 1H, *J* = 6.23 Hz), 7.97 (d, 2H, *J* = 6.21 Hz), 7.06 (d, 2H, *J* = 6.21 Hz), 6.90 (t, 1H, *J* = 6.23 Hz), 5.33 (1H, s), 5.20 (s, 2H), 4.81 (s, 1H), 2.90 (d, 2H, *J* = 6.21 Hz), 2.31 (d, 2H, *J* = 6.21 Hz), 2.00 (m, 4H), 1.84 (s, 6H), 1.70 (s, 3H); ^{13}C NMR (300 MHz): 198.9, 135.4, 132.0, 127.1, 123.5, 123.1, 151.0, 129.2, 122.8, 133.2, 136.7, 133.1, 128.8, 126.6, 51.1, 43.2, 39.7, 31.0, 26.4, 24.6, 18.6, 16.4; EI-MS (m/z): 347.22 (M^+,28%); Elemental analysis: Calcd. For ($C_{24}H_{29}NO$): C, 82.95; H, 8.41; N, 4.03%; Found: C, 82.96; H, 8.42; N, 4.05%.

2.1.3. 5,9-Dimethyl-1-phenyl-3-(p-tolylamino)deca-4,8-dien-1-one (**1c**)

Yield 84%; mw: 361.52; mp: 197 °C; IR (cm^{-1}): 3350, 3166, 2720, 1621; ^{1}H NMR (300 MHz): δ 9.46 (1H, s), 8.26 (1H, s), 7.97 (2H, d, *J* = 6.21Hz), 7.53 (2H, t, *J* = 6.23), 7.63 (1H, t, *J* = 6.23 Hz), 7.15 (2H, d, *J* = 6.21 Hz), 6.71 (2H, d, *J* = 6.21 Hz), 5.33 (1H, s), 5.20 (1H, s), 4.85 (1H, s), 2.94 (2H, d, *J* = 6.21 Hz), 2.00(4H, m), 2.34(3H, s), 1.82(6H, s), 1.70(3H, s); ^{13}C NMR (300 MHz, DMSO-d_6): 197.4, 135.5, 132.0, 127.7, 123.5, 148.0, 131.6, 129.5, 113.1, 136.7, 133.1, 128.8, 126.6, 51.5, 45.6, 39.7, 26.4, 24.6, 21.3, 18.6, 16.4; EI-MS (m/z): 361.24 (M^+,20%); Elemental analysis: Calcd. For ($C_{25}H_{31}NO$): C, 83.06; H, 8.64; N, 3.87%; Found: C, 83.08; H, 8.66; N, 3.88%.

2.1.4. N-(5,9-Dimethyl-1-oxo-1-phenyldeca-4,8-dien-3-yl)benzamide (**1d**)

Yield 86%; mw: 375.50; mp: 186 °C; IR (cm^{-1}): 3352, 3168, 2722, 1623; ^{1}H NMR (300 MHz): δ 9.44 (1H, s), 7.97 (2H, d, *J* = 6.21 Hz), 7.53 (2H, t, *J* = 6.23), 7.63 (1H, t, *J* = 6.23 Hz), 8.03 (2H, d, *J* = 6.21 Hz), 7.63 (2H, t, *J* = 6.23 Hz), 7.70 (1H, t, *J* = 6.23 Hz), 5.33 (1H, s), 5.20 (1H, s), 3.86 (1H, s), 2.96 (2H, d, *J* = 6.21 Hz), 2.00 (4H, m), 1.85(6H, s), 1.70 (3H, s); ^{13}C NMR (300 MHz): 197.4, 167.5, 135.9, 132.0, 127.7, 123.5, 134.2, 132.1, 128.8, 127.5, 136.7, 133.1, 128.8, 126.6, 50.7, 43.1, 39.7, 26.4, 24.6, 18.6, 16.4; EI-MS (m/z): 376.22 (M^+,27%); Elemental analysis: Calcd. For ($C_{25}H_{29}NO_2$): C, 79.96; H, 7.78; N, 3.73%; Found: C, 79.94; H, 7.80; N, 3.71%.

2.1.5. 3-(2-Benzylidenehydrazinyl)-5,9-dimethyl-1-phenyldeca-4,8-dien-1-one (**1e**)

Yield 82%; mw: 374.52; mp: 188 °C; IR (cm^{-1}): 3354, 3170, 2720, 1621, 1540; ^{1}H NMR (300 MHz): δ 9.40 (1H, s), 8.54 (1H, s), 7.97 (2H, d, *J* = 6.21 Hz), 7.53 (2H, t, *J* = 6.23), 7.63 (1H, t, *J* = 6.23 Hz), 7.83 (2H, d, *J* = 6.21 Hz), 7.52 (3H, m), 5.35 (1H, s), 5.20 (1H, s), 3.81 (1H, s), 2.94 (2H, d, *J* = 6.21 Hz), 2.00 (4H, m), 1.81 (6H, s), 1.70 (3H, s); ^{13}C NMR (300MHz, DMSO-d_6): 197.1, 143.3, 135.7, 132.0, 127.9, 123.5, 136.7, 133.1, 128.8, 128.6, 133.7, 131.0, 129.2, 128.8, 50.0, 48.8, 39.7, 26.4, 24.6, 18.6, 16.4; EI-MS (m/z): 374.24 (M^+,27%); Elemental analysis: Calcd. For ($C_{25}H_{30}N_2O$): C, 80.17; H, 8.07; N, 7.48%; Found: C, 80.15; H, 8.08; N, 7.50%.

2.1.6. 5,9-Dimethyl-1-phenyl-3-(2-(3-phenylallylidene)hydrazinyl)deca-4,8-dien-1-one (**1f**)

Yield 89%; mw: 400.56; mp: 179 °C; IR (cm^{-1}): 3356, 3172, 2722, 1623, 1542; ^{1}H NMR (300 MHz): δ 9.36 (s, 1H), 7.50 (s, 1H), 7.97 (2H, d, *J* = 6.21Hz), 7.53 (2H, t, *J* = 6.23), 7.63 (1H, t, *J* = 6.23 Hz), 7.60 (2H, d, *J* = 6.21 Hz), 7.40 (2H, t, *J* = 6.23 Hz), 7.33 (1H, t, *J* = 6.23 Hz), 7.22 (1H, s,), 6.85 (1H, d, *J* = 6.21 Hz), 5.33 (1H, s), 5.20 (1H, s), 3.81(1H, s), 2.94 (2H, d, *J* = 6.21 Hz), 2.00 (4H, m), 1.87(6H, s), 1.70(3H, s); ^{13}C NMR (300 MHz): 197.0, 137.2, 136.1, 135.1, 131.9, 127.7, 126.3, 123.5, 136.7, 135.2, 134.1, 128.8, 128.6, 128.9, 127.9, 127.2, 50.8, 48.8, 39.7, 26.1, 24.1, 18.2 16.4; EI-MS (m/z): 400.25 (M^{+},30%); Elemental analysis: Calcd. For ($C_{27}H_{32}N_2O$): C, 80.96; H, 8.05; N, 6.99%; Found: C, 80.95; H, 8.08; N, 6.96%.

2.2. Biological Activities

2.2.1. Larvicidal Activity

Culex quinquefasiatus eggs were collected from the drainage system. Hatching eggs were kept in clean water at room temperature. After seven days larval development was tracked. Larvae collected at the tip of a pasture pipette were placed in cotton buds in order to remove excess water. The cotton buds were then transferred to test vials (ten/vial). We observed larval mortality at various concentrations of 10, 25, 50, and 100 µg/mL, including positive (with 2% ethanol) and negative controls (without vehicle) according to a procedure described previously [21,22]. We measured mortality in terms of ratios (%) of dead vs. live larvae caused by the compounds. Probit scale analysis was used to calculate the LD_{50} values. After exposure for 24 h, the number of larvae still alive was counted. This was repeated three times to ensure that the results would hold up statistically.

2.2.2. Antifeedant Activity

The antifeedant activity was evaluated to study the effect of larvicides against non-target aquatic species. In order to evaluate the antifeedant activity, samples were tested at concentrations of 10, 25, 50, and 100 µg/mL, in conjunction with positive and negative controls (with 2% ethanol) and evaluated on marine fingerlings (*O. mossambicus*).

The tested compounds were dissolved in 1000 mL water containing five fingerlings in each experimental and control glass bowl. After six hours, mortality was measured continuously and at 1 h intervals for the next 12 h. A ratio (%) of the numbers of dead vs. live fingerlings was used to assess the mortality caused by the compounds (as described previously [21,22]).

2.2.3. Statistical Analysis

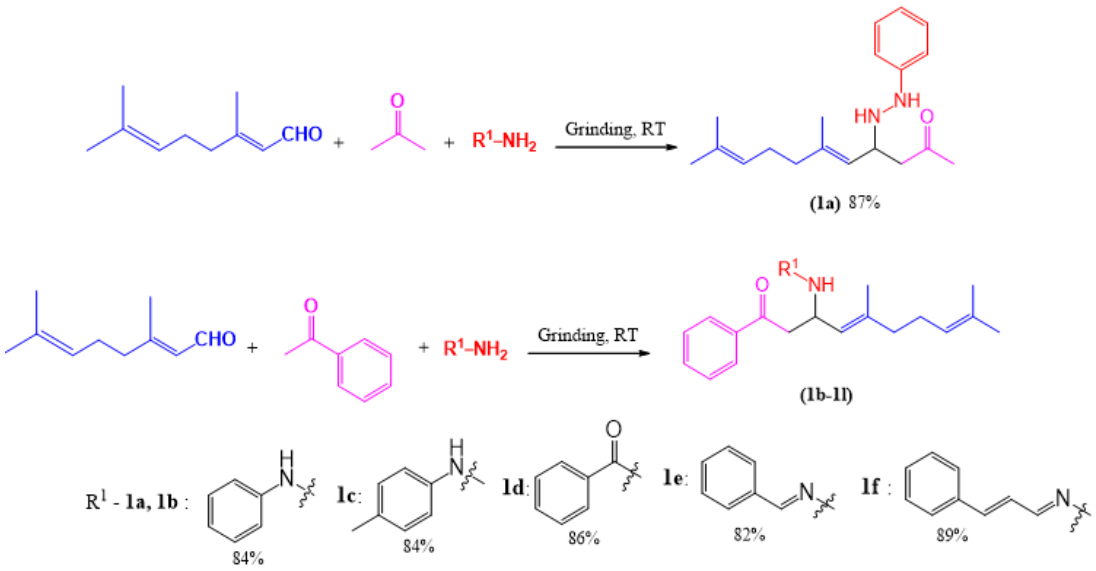
With Microsoft Excel, we calculated standard deviations (SD) based on at least three independent assessments for each LD_{50} value.

3. Results and Discussion

The grindstone method was used to synthesize geranylacetones of the title compounds. A mixture of citral, aceotone, substituted amine were ground together in a mortar and pestle. This was then followed by purification via column chromatography on silica with Ethyl acetate:hexane (4:6) as the mobile phase. Scheme 1 shows a synthetic route for the preparation of geranylacetone derivatives. The compounds were obtained up to 88–92% yield. FT-IR, ^{1}H, and ^{13}C NMR spectroscopy were used to analyze the compounds obtained (see Supplementary Information). Each compound (**1a**–**1f**) was analyzed for their solubility in ethanol and water. All compounds were found to be completely soluble in ethanol. The solubility of geranylacetones in water is 8.867 mg/L at 25 °C and 0.1 mg/5 mL in 2% of ethanol. The dissolution rates of compound **1f** are 2.13 mg/L of water and 0.15 mg/5 mL in the case of 2% of ethanol.

The compounds were assigned by their IR spectra and were found to have significant resonances at 3350.23–3356.54, 2720.45–2726.98, and 1621.68–1627.70 cm^{-1} corresponding to the -NH, CH starching in phenyl ring, and –C=O groups, respectively. The ^{1}H NMR spectrum included signals at δ 9.36–9.46, 3.81–4.81, 5.20–5.35, and 1.81–1.87 ppm, indicating

-NH, -CH, –C=CH, and =C-CH_3 protons, respectively. The ^{13}C NMR spectrum has peaked in the range of δ 197.0–207.7, 50.0–54.3, 121.5–127.9, and 135.1–135.9 ppm, which conforms to -C=O, -CH, =CH, and -HC= atoms, respectively. The ^{1}H and ^{13}C NMR spectrum of compounds (**1a**–**1f**) are shown in Figures S1–S12 in the Supplementary Materials. For all of these compounds, mass spectra and elemental analysis were used to determine their conformation.



Scheme 1. Synthetic route of geranylacetone derivative (**1a**–**1f**).

Biological Activity

We studied six compounds (**1a**–**1f**) against the second instar larvae of *C. quinquefasciatus*. In view of the structure-activity relationships, the final compounds contained geranylacetone with various types of amines, thus exerting larvicidal and toxic effects depending on their chemical compositions.

The larvicidal activity of geranylacetone derivatives has never been studied before, yet other bioactivities of geranylacetone are scarce in the literature [23,24], and it also appears monoterpenes such as geranylacetone have no water-polluting properties. In addition, its antifeedant actives (Ichthyotoxicity) have not been reported.

Figure 2 shows that the structure-activity relationship for geranylacetone and their derivatives in both larvicidal and Ichthyotoxicity activities. Compound **1f** showed higher larvicidal activity than other compounds, with an LD_{50} of 14.1 µg/mL, which was also higher than those of the other natural products. Compounds **1f** induced a mortality rate of 100% at 100 µg/mL concentration and 13.9% of mortality in the test fish, *O. mossambicus* with respect to the antifeedant activity. This suggests that the presence of keto and hydrazine groups may be the reason for the observed biological effects, respectively. Compound **1a** shows a mortality rate of 92% with LD_{50} values of 42.0 µg/mL, whereas it resulted in 26.1% mortality in the case of antifeedant screening. Compound **1f** induced 100% mortality at 100 µg/mL and 13.9% antifeedant activity due to the presence of acetophenone and hydrazine groups causing biological effects. Other compounds **1b**, **1c**, **1d**, and **1e** show that around 97.3 to 100% of mortality in larvicidal screening with LD_{50} values around 18.6 to 35.6 µg/mL suggesting the presence of different types of hydrazine as the reason for the observed biological effects. On the other hand, this set of compounds exhibited some toxic behavior in the range of 23.1 to 33.4 µg/mL compared to **1a**, **1f**, and geranylacetone. The larvicidal screening results showed that compound **1f** is significantly active. The percentages of mortality and LD_{50} values are presented in Tables 1 and 2, respectively. Figure 3 indicates the GC-MS of the compound geranylacetone, which shows that it is highly pure and has a molecular ion peak at 194 m/z. In Figure 4, compound **1f**

shows high purity with a mass spectrum of molecular ion corresponding to 400.56 m/z, which is confirmatory of synthesized compounds.

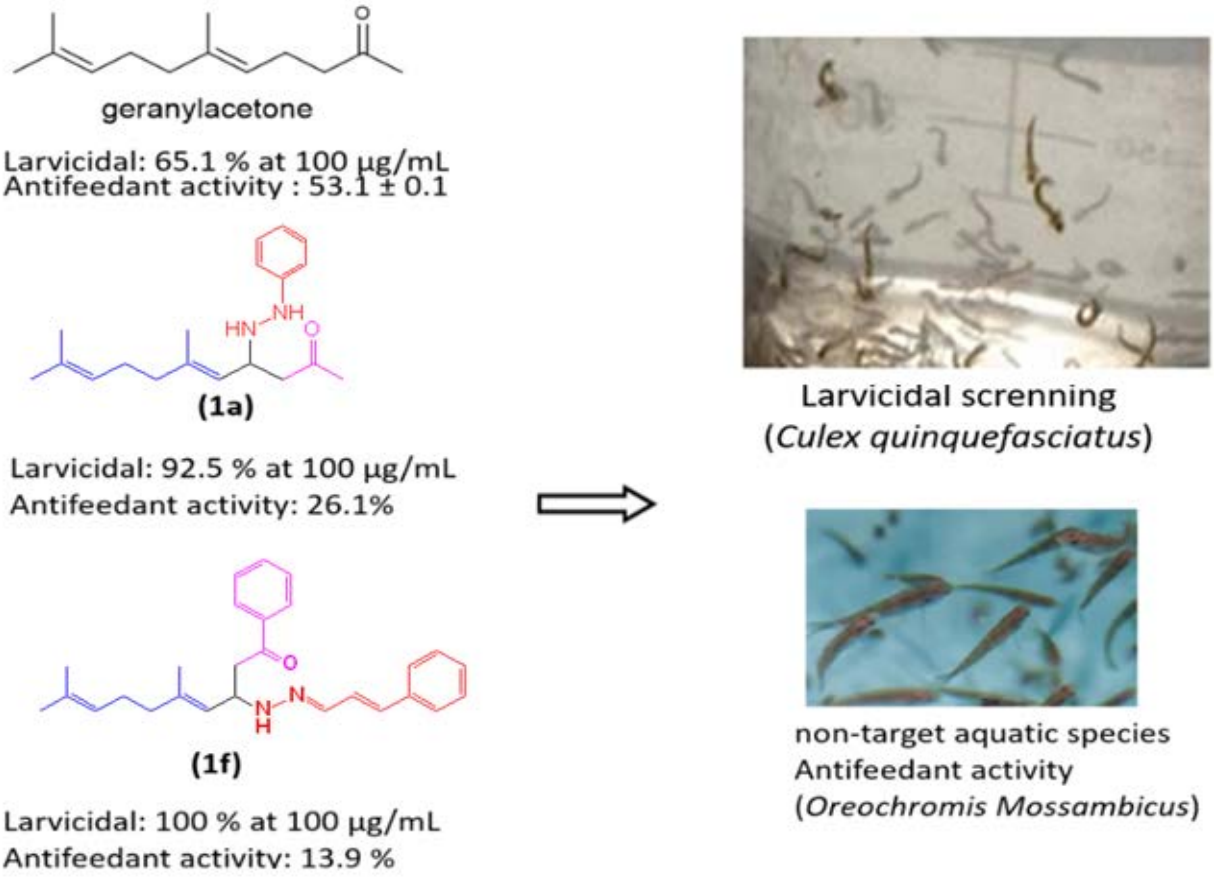


Figure 2. Structural relationship of geranylacetone derivatives.

Table 1. Larvicidal effects of compounds (**1a**–**1f**).

Compounds	% of Mortality			LD_{50} (µg/mL) [a]
	25 µg/mL	50 µg/mL	100 µg/mL	
Geranylacetone	29.8 ± 0.6	42.6 ± 0.2	65.1 ± 0.4	67.2
1a	32.7 ± 0.6	62.3 ± 0.4	92.5 ± 0.8	42.0
1b	37.6 ± 0.8	67.3 ± 0.13	97.3 ± 0.1	35.6
1c	46.2 ± 0.1	82.9 ± 0.2	100 ± 0.0	18.6
1d	40.1 ± 0.3	81.3 ± 0.1	99.1 ± 0.2	25.9
1e	38.8 ± 0.9	68.6 ± 0.12	98.7 ± 0.3	34.2
1f	48.0 ± 0.3	86.1 ± 0.3	100 ± 0.0	14.1
Negative control	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

[a] Values are mean ± SD (n = 3). Negative control—2% of ethanol.

Table 2. Compounds (**1a**–**1f**) exhibit antifeedant activity.

Compounds	% of Mortality at 25 µg/mL	% of Mortality at 50 µg/mL	% of Mortality at 100 µg/mL	LD_{50} (µg/mL) [a]
Geranylacetone	20.0 ± 0.0	32.5 ± 0.2	53.1 ± 0.1	92.2
1a	9.2 ± 0.5	15.2 ± 0.1	26.1 ± 0.1	>100
1b	8.2 ± 0.2	15.1 ± 0.6	33.4± 0.32	>100
1c	5.5 ± 0.3	11.1 ± 0.7	23.1 ± 0.4	>100
1d	7.2 ± 0.7	14.2 ± 0.9	26.2 ± 0.1	>100
1e	8.2 ± 0.2	15.1 ± 0.6	33.4± 0.32	>100
1f	3.0 ± 0.1	6.21 ± 0.1	13.9 ± 0.2	>100
Negative control	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0	0.0 ± 0.0

[a] Values are mean ± SD (n = 3). Negative control—2% of ethanol.

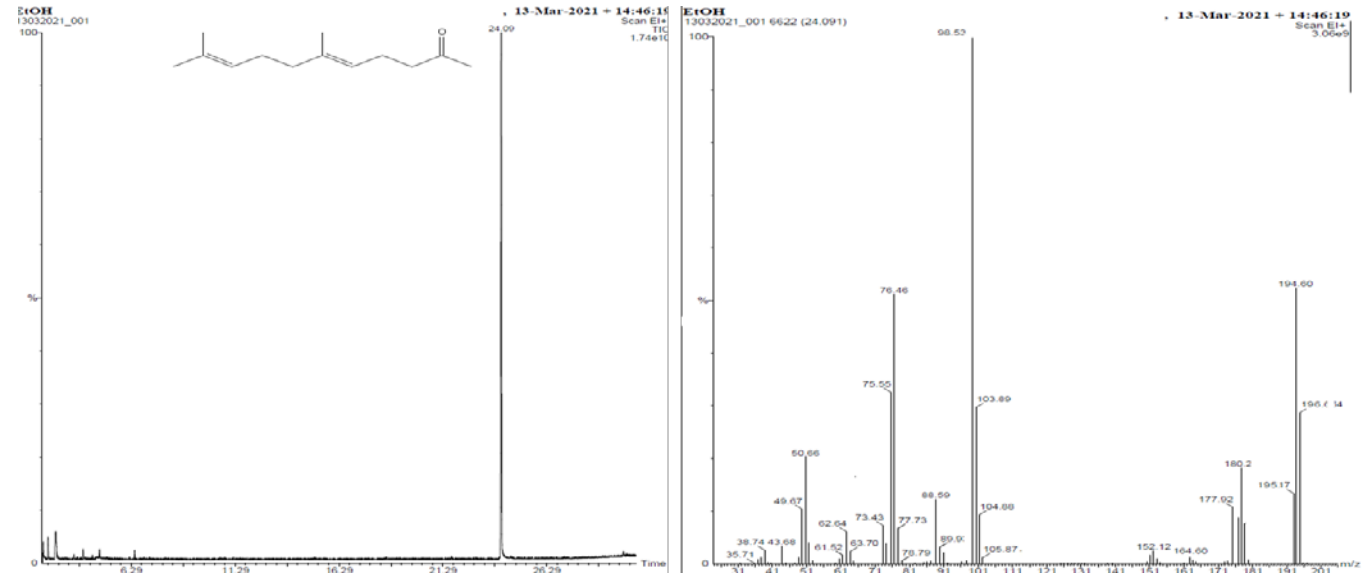


Figure 3. GC-MS analysis of geranylacetone.

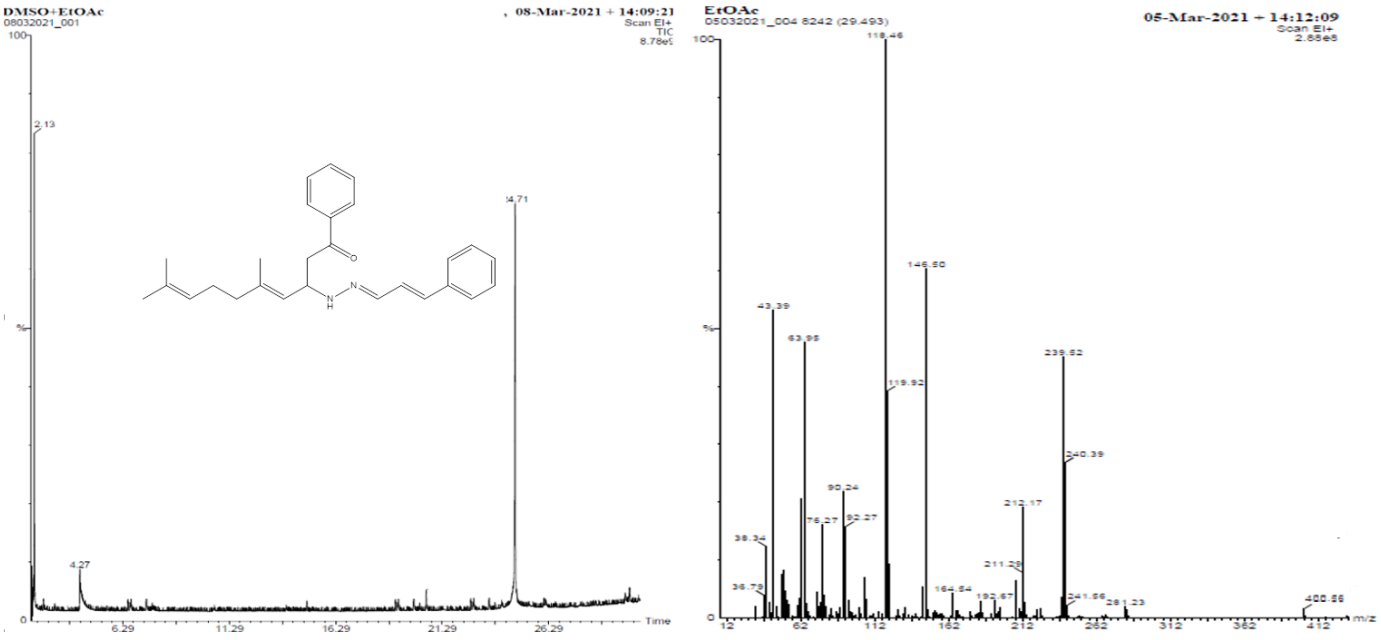


Figure 4. GC-MS analysis of compound **1f**.

4. Conclusions

The grindstone method was used to synthesize new larvicidal geranylacetone derivatives using a Mannich base, resulting in high yields. Compounds were tested against *Culex quinquefasciatus* and *Oreochromis mossambicus*. Results of antifeedant activities showed that compound **1f** induced 13.9% mortality within 24 h against *Oreochromis mossambicus* and *Culex quinquefasciatus* (LD_{50} = 14.1 g/mL). Based on the results, compound **1f** is the most efficient insecticide, and the compounds outlined in this paper can be used to develop eco-friendly pesticides and biopharmaceuticals.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/agronomy11112342/s1, Figures S1–S12: Larvicidal activity of geranylacetone derivatives against *Culex quinquefasciatus* larvae and investigation of environmental toxicity and non-target aquatic species.

Author Contributions: Formal analysis, M.A.-Z. and M.S.A.-E.; methodology, R.S.; software, D.A.; Investigation, A.I.; Data curation, H.A.R.; Writing-review and editing, S.A.; Supervision, A.I. All authors have read and agreed to the published version of the manuscript.

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Data Availability Statement: Data used to support the findings of this study are available from the corresponding author.

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Conflicts of Interest: There is no conflict of interest among the authors.

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