Exploring the growth inhibition potential of monoketone curcuminoids against *Spodoptera frugiperda*

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ABSTRACT. *Spodoptera frugiperda*, known as the fall armyworm (FAW), is a polyphagous pest that causes huge economic losses in different agricultural regions of the world. Its control is challenging due to its widespread resistance to conventional insecticides and *Bt events*. This study aimed to assess the lethal toxicity and growth-inhibitory effects of eight acetone-derived monoketone curcuminoids (MKCs) on *S. frugiperda* larvae. MKCs were synthesized by Claisen-Schmidt condensation between acetone and aromatic aldehydes in a basic medium and tested against FAW larvae at a concentration of 250 mg kg-1 (dietary exposure) over 7 days. None of the tested compounds showed a significant lethal toxicity to FAW. However, halogenated MKCs derivatives 4 ((1E,4E)-1,5-bis(4-fluorophenyl)penta-1,4-dien-3-one) and 5 ((1E,4E)-1,5-bis(4-chlorophenyl)penta-1,4-dien-3-one) exhibited sublethal effects, reducing larval weight by 59% and 55%, respectively, compared to the negative control. These results indicated that the halogenation of MKCs may be a promising strategy to be exploited in the search for novel bioactive compounds to manage FAW in agricultural food production systems.

Key words: Claisen-Schmidt condensation; diarylpentanoids; fall armyworm; halogenated compounds

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INTRODUCTION

The fall armyworm (FAW), *Spodoptera frugiperda* (J. E. Smith) (Lepidoptera: Noctuidae), is a pest that primarily affects corn, soybeans, and cotton crops. In the southeastern United States, FAW causes losses of $60 million annually, while in Brazil, a reduction of ~ 34% in corn productivity due to their damage was estimated, which is equivalent to about 400 million dollars every year (Kartakis et al., 2025). The high economic impact caused by FAW is due to its polyphagous habit, which allows it to feed on more than 350 plant species (Montezano et al., 2018). This characteristic contributes to its wide adaptation and persistence in diverse agroecosystems (Chaudhary et al., 2025).

FAW is native to the tropical and subtropical regions of the Americas, but has expanded rapidly, currently being recorded in more than 100 countries on different continents (Chaudhary et al., 2025). The life cycle of FAW varies according to local environmental conditions, beginning with the laying and hatching of eggs, followed by six larval instars, the pupal stage, and finally, adult emergence. Among the developmental stages, the larval phase stands out for its economic importance, as larvae exhibit a high capacity for leaf consumption and destructive potential over various crops. The complete biological cycle can be completed within approximately 30 to 90 days, depending on temperature conditions and food availability (Navasero & Navasero, 2020).

The control of this agricultural pest using various chemical insecticides has proven to be highly effective and easy to apply, providing satisfactory results and making these products highly valued in the agricultural market (Paredes-Sanchez et al., 2021). In Brazil, about 460 formulated insecticides for the chemical control of *S. frugiperda* are registered, including pyrethroids, carbamates, organophosphates, spinosyns, and diamides (Agrofit, 2026). However, the indiscriminate use of these products can result in the selection of resistant populations and, consequently, in the increase of pest damage and population abundance (Paredes-Sanchez et al., 2021). In this context, the

development of new and more sustainable and efficient tools for the control of *S. frugiperda* within an integrated pest management (IPM) approach becomes fundamental for food security and the competitiveness of the agricultural sector in intensive systems, including regions of climatic and socioeconomic vulnerability (Tay et al., 2023).

Some plants stand out for their insecticidal potential against agriculturally relevant arthropod pests, such as *Curcuma longa* L. (Zingiberaceae), which is recognized for its nematicidal, larvicidal, and oviposition deterrent properties on insect pests from different orders (Ajaiyeoba et al., 2008; Verma et al., 2018; Rashid et al., 2021; Zhou et al., 2021). Curcumin (or diferuloylmethane, **I**), demethoxycurcumin (**II**), and *bis*-demethoxycurcumin (**III**), the main active constituents from *C. longa* rhizomes, are known as 'curcuminoids'. The term 'monoketone curcuminoids' (or monocarbonyl curcuminoids) has been used to refer to some diarylpentanoids formed through a Claisen-Schmidt condensation between an aromatic aldehyde and an aliphatic or alicyclic ketone. Because these compounds are considered analogs to the diarylpentanoid structure of curcumin, they have been extensively synthesized and studied to overcome some limitations of curcumin, such as its low bioavailability (Gagandeep et al., 2020) and to enhance its pharmacokinetic properties (Vieira et al., 2024).

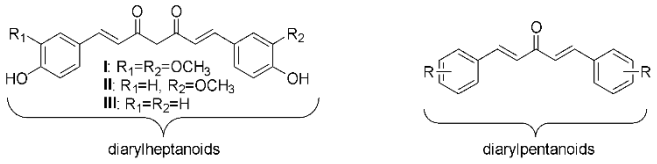


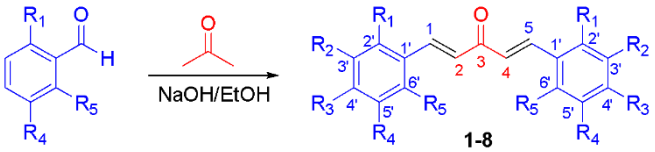
Figure 1. Chemical structures of the diarylheptanoids curcumin (**I**), demethoxycurcumin (**II**), and bisdemethoxycurcumin (**III**), and the basic structure of diarylpentanoids or acetone-derived 'monoketone curcuminoids' (MKCs).

Previous studies have demonstrated the potential of monocarbonyl curcuminoids in various biological activities, including antitumor, anti-inflammatory, antioxidant, and antiparasitic effects (Prasad et al., 2011; Mohd Faudzi et al., 2015; Dohutia et al., 2017; Nivedha et al., 2022). However, reports on their insecticidal activity are scarce, being mainly limited to mosquitocidal and larvicidal effects (Matiadis et al., 2021; Ioannou et al., 2025). Therefore, this study aimed to assess the lethal toxicity and growth inhibitory effects of a series of acetone-derived monoketone curcuminoids (MKCs) on FAW larvae.

MATERIAL AND METHODS

Synthesis of acetone-derived monoketone curcuminoids

The MKCs were obtained through Claisen-Schmidt condensation between acetone and an aromatic aldehyde in a basic medium (Scheme 1), as previously reported (Vieira et al., 2018). Briefly, the reaction medium was prepared by adding 2.5 mol L^{-1} aqueous sodium hydroxide (NaOH) solution and 20 mL of ethanol (EtOH), which was transferred to a 100 mL flask containing acetone (13 mmol) and the aromatic aldehyde (26 mmol). The reaction mixture was stirred at 0 °C for a period ranging from 30 min to 24 h, depending on the aldehyde used. Next, the formed precipitate was vacuum-filtered, purified by recrystallization from a hexane:ethanol mixture, and then dried under vacuum. The obtained compounds, numbered 1 to 8, were identified by NMR spectroscopy and mass spectrometry, and their yields and reaction times were also determined.



	1	2	3	4	5	6	7	8
R_1	H	H	H	H	H	H	H	OMe
R_2	H	H	H	H	H	H	OMe	H
R_3	H	Me	NH_2	F	Cl	Br	OMe	OMe
R_4	H	H	H	H	H	H	OMe	H
R_5	H	H	H	H	H	H	H	OMe
time (h)	0.5	1	3	2	1.5	2	2	24
yield (%)	61	82	67	55	64	65	83	97

Scheme 1. Synthesis, structures, and yields of MKCs **1-8**.

Structure identification of MKCs 1-8

Compounds **1-8** were identified by nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry through comparison of the obtained data with those described in the literature. To this end, the samples were dissolved in $CDCl_3$ for spectroscopic analyses. ^1H and ^{13}C NMR spectra were acquired using a Bruker DRX400 spectrometer, operating at 400 MHz and 100 MHz, respectively. Mass spectra were obtained using a Shimadzu GCMS 2010 plus chromatograph equipped with an Rtx-5 MS column and an electron impact ionization (EI-MS) source operating at 70 eV, or on a triple quadrupole MS equipment (QqQ) Xevo TQS (Waters, Milford, MA, USA) equipped with Z-spray operating in the positive ion mode. All the NMR (^1H and ^{13}C) and mass spectra are provided in the Supporting Information.

Tested insects

The population of FAW used in the bioassays was obtained from rearing established with insects collected in cornfields in the region of Chapecó, SC, Brazil (27°05′19″S; 52°38′13″W), and kept under laboratory conditions (temperature 25±2°C, Relative Humidity (RH) 60±10%, and a photophase of 14 h). For

maintenance, caterpillars were placed individually in 50 mL plastic containers and fed with an artificial diet (Greene et al., 1976) until pupa formation. The adults that emerged were distributed in PVC cages where they received a 10% (w/v) honey solution as a food source.

Bioassay (dietary exposure)

All bioassays were carried out under controlled laboratory conditions (temperature 25±1°C, RH 60±10%, and a photophase of 14 h) in a completely randomized design.

The effects of pure compounds were evaluated at a concentration of 250 mg kg^{-1}, defined according to previous tests. For this purpose, the compounds were solubilized in 2 mL of ethyl acetate and incorporated into 100 g of artificial diet (Ansante et al., 2015) at a temperature below 50°C to avoid the degradation of thermolabile compounds. As a positive control, we used a commercial insecticide based on chlorantraniliprole (Premio® 20 SC, FMC Química do Brasil Ltda., Barueri, SP, Brazil) incorporated at the recommended rate for the control of FAW in maize crops in Brazil (MAPA, 2026). Furthermore, two negative controls were established: distilled water and ethyl acetate, both at the same volume (2 mL) used for solubilization of the positive control and the pure compounds, respectively.

After incorporating the treatments into the artificial diet, the treated diet was deposited in a sterilized Gerbox®. After 24 h (the time required to evaporate the excess water from the medium), the treated diet was cut into small pieces (1 × 1 cm) and put individually in twenty-four-well enzyme-linked immunosorbent assay (ELISA) plates (Techno Plastic Products AG®, Trasadingen, Canton of Schaffhausen, Switzerland), with each well infested with one neonate FAW-larva (<24 h old), that is, first-instar larva. For this purpose, each treatment consisted of six replicates, each containing 24 individual first-instar larvae, totaling 144 caterpillars per treatment.

The evaluation of the mortality of caterpillars exposed to different treatments was performed daily for seven days. After the seventh day of exposure, the weights of the surviving caterpillars were also examined.

Data analyses

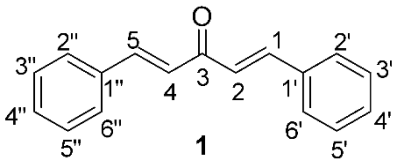
Generalized linear models (GLM) (Nelder & Wedderburn, 1972) with quasibinomial and Gaussian distributions were used for the analyses of mortality (proportion) and larval weight, respectively. The verification of quality adjustment was performed through the half-normal plot with simulation envelope (Hinde & Demétrio, 1998). When there were significant differences among treatments, multiple comparisons (Tukey's *post hoc* test, $p<0.05$) were performed using the glht function by means of multcomp package, with adjustment of *p*-values. All analyses were performed using the "R" statistical software version 4.0.2 (R Core Team, 2020).

RESULTS AND DISCUSSION

Synthesis of MKCs 1-8

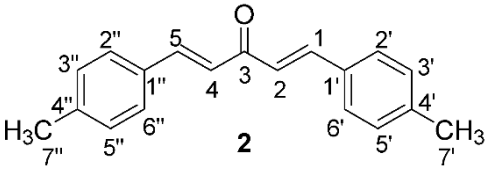
MKCs **1-8** were obtained as solids in yields ranging between 55 and 97% (Scheme 1). Their ^{1}H and ^{13}C NMR and mass spectral data are listed in Chart 1, and the corresponding spectra are given in the Supporting Information.

Chart 1. ^{1}H and ^{13}C NMR and mass spectral data of MKCs **1-8**



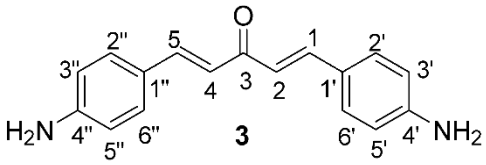
1

(1*E*,4*E*)-1,5-diphenylpenta-1,4-dien-3-one (**1**). Yellowish solid, 61% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.10 (2H, *d*, $J_{4,5=2,1}$ = 16.0 Hz, H4=H2), 7.41 (6H, *m*, H3′=H3″=H5′=H5″, and H6′=H6″), 7.62 (2H, *m*, H4′=H4″), 7.76 (2H, *d*, $J_{5,4=1,2}$ = 16.0 Hz, H1=H5). ^{13}C NMR (100 MHz, $CDCl_3$): 125.6 (C2=C4), 128.5 (C2′=C2″=C6′=C6″), 129.1 (C3′=C5′=C3″=C5″), 130.6 (C4′=C4″), 135.0 (C1′=C1″), 143.5 (C1=C5), 189.1 (C3). EI-MS (*m/z*, relative intensity): 234 (100%, $M^{\bullet+}$), 131 (40%, $[M\text{-}C_8H_7^{\bullet}]^+$), 103 (65%, $[M\text{-}C_8H_7^{\bullet}\text{-}CO]^+$), 77 (50%, $C_6H_5^+$).



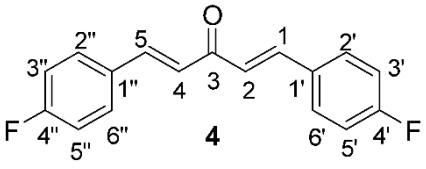
2

(1*E*,4*E*)-1,5-di-*p*-tolylpenta-1,4-dien-3-one (2). Yellow solid, 82% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 2.55 (6 H, *s*, 4′-CH_3), 7.07 (2 H, *d*, $J_{4,5=2,1}$= 16.0 Hz, H2=H4), 7.25 (4 H, *d*, $J_{5'6'=5'',6''=3',2'=3'',2''}$ = 8.0 Hz, H3′=H3″=H5′=H5″), 7.54 (4 H, *d*, $J_{6',5'=6'',5''=2',3'=2'',3''}$ = 8.0 Hz, H6′=H6″=H2′=H2″), 7.75 (2 H, *d*, $J_{5,4=1,2}$ = 16.0 Hz, H1=H5). ^{13}C NMR (100 MHz, $CDCl_3$): 21.6 (4′-CH_3), 124.8 (C2=C4), 128.5 (C2′=C2″=C6′=C6″), 129.8 (C3′=C3″=C5′=C5″), 132.3 (C1′=C1″), 141.1 (C4′=C4″), 143.3 (C1=C5), 189.2 (C3). EI-MS (*m/z*, relative intensity): 262 (65%, $M^{\bullet+}$), 261 (45%, $[M\text{-}H^{\bullet}]^+$), 247 (100%, $[M\text{-}CH_3^{\bullet}]^+$), 115 (50%, $C_9H_7^+$).



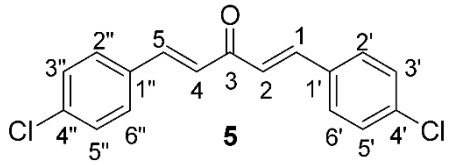
3

(1*E*,4*E*)-1,5-*bis*(4-aminophenyl)penta-1,4-dien-3-one (3). Orange solid, 67 % yield. ^{1}H NMR (400 MHz, CD_2Cl_2): 6.68 (4 H, *d*, $J_{3',2'=5',6'}$= 8.0 Hz, H3′=H3″=H5′=H5″), 6.88 (2 H, *d*, $J_{4,5=2,1}$= 16.0 Hz, H2=H4), 7.66 (4 H, *d*, $J_{2',3'=6',5'}$ = 8.0 Hz, H2′=H2′′=H6′=H6′′), 7.05 (2 H, *d*, $J_{5,4=1,2}$ = 16.0 Hz, H1=H5). ^{13}C NMR (100 MHz, CD_2Cl_2): 112.1 (C3′=C3′′=C5′=C5′′), 121.5 (C2=C4), 123.2 (C1=C1′), 130.2 (C2′=C2′′=C6′=C6′′), 143.0 (C1=C5), 151.9 (C4=C4′), 189.0 (C3). ESI(+)-MS (*m/z*, relative intensity): 297 (25 %, $[M+Na]^+$), 265 (100 %, $[M+H]^+$)



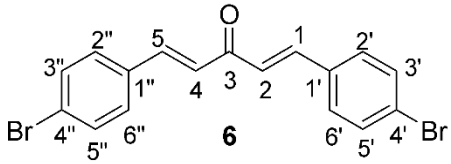
4

(1*E*,4*E*)-1,5-*bis*(4-fluorophenyl)penta-1,4-dien-3-one (4). White solid, 55% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.05 (2 H, *d*, $J_{4,5=2,1}$= 16.0 Hz, H2=H4), 7.32 (4 H, *d*, $J_{3',2'=5',6'}$= 8.0 Hz, H3′=H3″=H5′=H5″), 7.39 (4 H, *d*, $J_{2',3'=6',5'}$ = 8.0 Hz, H2′=H6′), 7.69 (2 H, *d*, $J_{5,4=1,2}$ = 16.0 Hz, H1=H5). ^{13}C NMR (100 MHz, CD_2Cl_2): 114.7 (C3′=C3′′=C5′=C5′′), 126.5 (C2=C4), 130.6 (C2′=C2′′=C6′=C6′′), 137.7 (C1′), 142.3 (C1=C5), 164.2 (C4=C4′), 188.4 (C3). EI-MS (*m/z*, relative intensity): 270 (20%, $M^{\bullet+}$), 149 (30%, $M^{\bullet+}$-$C_8H_6F^{\bullet}$), 121 (55%, $M^{\bullet+}$-$C_8H_6F^{\bullet}$-CO), 101 ($C_8H_5^+$, 100%).



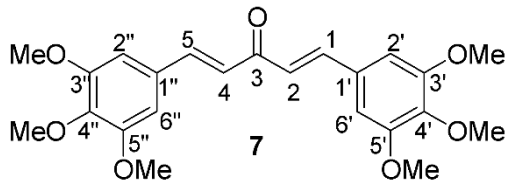
5

(1*E*,4*E*)-1,5-*bis*(4-chlorophenyl)penta-1,4-dien-3-one (5). Yellowish solid, 64% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.05 (2 H, *d*, $J_{4,5=2,1}$= 16.0 Hz, H2=H4), 7.39 (4 H, *d*, $J_{3',2'=5',6'}$= 8.0 Hz, H3′=H3″=H5′=H5″), 7.55 (4 H, *d*, $J_{2',3'=6',5'}$ = 8.0 Hz, H2′=H6′), 7.68 (2 H, *d*, $J_{5,4=1,2}$ = 16.0 Hz, H1=H5). ^{13}C NMR (100 MHz, $CDCl_3$): 126.1 (C2=C4), 129.4 (C3′=C3′′=C5′=C5′′), 129.7 (C2′=C2′′=C6′=C6′′), 133.4 (C1′=C1′′), 136.7 (C4′=C4′′), 142.2 (C1=C5), 188.7 (C3). EI-MS (*m/z*, relative intensity): 302/304/306 (75 %, 9:6:1, $M^{\bullet+}$, $M^{\bullet+}$+1, $M^{\bullet+}$+2), 267 (80 %, $[M-Cl^{\bullet}]^+$), 101 (100 %, $C_8H_5^+$)



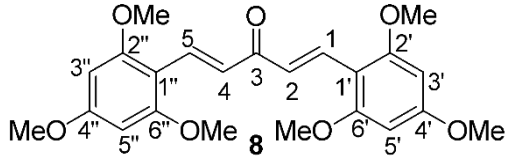
6

(1*E*,4*E*)-1,5-*bis*(4-bromophenyl)penta-1,4-dien-3-one (6). Yellowish solid, 65% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 7.05 (2H, *d*, $J_{2,1=4,5}$= 16.0 Hz, H2=H4), 7.48 (4H, *d*, $J_{2',3'=5',6'}$ = 8.4 Hz, H2′=H2′′=H6′=H6′′), 7.56 (4 H, *d*, $J_{3',2'}$ =8.4 Hz, H3′=H3″=H5′=H5″), 7.67 (2H, *d*, $J_{1,2=5,4}$ = 16.0 Hz, H1=H5). ^{13}C NMR (100 MHz, $CDCl_3$): 125.1 (C4′=C4′′), 126.0 (C2=C4), 129.9 (C3′=C3′′=C5′=C5′′), 132.4 (C2′=C2′′=C6′=C6′′), 133.8 (C1′=C1′′), 142.3 (C1=C5), 188.5 (C3). EI-MS (*m/z*, relative intensity): 392/394/396 (1:2:1, $M^{\bullet+}$, $M^{\bullet+}$+2, $M^{\bullet+}$+4), 311/313 (30%, 1:1, $M^{\bullet+}$-Br$^{\bullet}$)



7

(1*E*,4*E*)-1,5-*bis*(3,4,5-trimethoxyphenyl)penta-1,4-dien-3-one (**7**). Yellow solid, 83% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 3.90 (18 H, *s*, 3′=4′=5′=OMe), 6.85 (4 H, *s*, H2′= H2″= H6′=H6″), 6.97 (2H, *d*, $J_{2,1=4,5}$=15.8 Hz, H2=H4), 7.66 (2 H, *d*, $J_{1,2=5,4}$ = 15.8 Hz, H1=H5). ^{13}C NMR (100 MHz, $CDCl_3$): 56.5 (3′′=3′=5′′=5′-OCH_3), 60.9 (4′=4′′-OCH_3), 106.1 (C2′=C2′′=C6′=C6′′), 125.2 (C2=C4), 130.6 (C1′=C1), 140.9 (C4′=C4′′), 143.8 (C1=C5), 153.9 (C3′=C3′′=C5′=C5′′), 188.9 (C3). ESI(+)-MS (*m/z*, relative intensity): 437 (100 %, $[M+Na]^+$), 415 (40 %, $[M+H]^+$)



8

(1*E*,4*E*)-1,5-*bis*(2,4,6-trimethoxyphenyl)penta-1,4-dien-3-one (**8**). Yellow solid, 97% yield. ^{1}H NMR (400 MHz, $CDCl_3$): 3.81 (6 H, s, 2′-OCH_3), 3.84 (12 H, *s*, 2′=2′′=4′=4′′-OCH_3), 6.12 (4 H, *s*, H3′=H3′′=H5′=H5′′), 7.08 (2H, *d*, $J_{2,1=4,5}$=16.5 Hz, H2=H4), 7.96 (2 H, *d*, $J_{1,2=5,4}$ = 16.5 Hz, H1=H5). ^{13}C NMR (100 MHz, $CDCl_3$): 55.8 (2′-OCH_3), 56.2 (4′=6′-OCH_3), 90.9 (C3′=C5′), 106.2 (C1′=C1′′), 128.0 (C2=C4), 135.4 (C1=C5), 161.9 (C2′=C6′), 163.5 (C4′=C4′′), 201.1 (C3). ESI(+)-MS (*m/z*, relative intensity): 437 (50 %, $[M+Na]^+$), 415 (100 %, $[M+H]^+$)

Lethal toxicity and growth inhibitory activities of MKCs 1-8 against FAW

After 168 h of exposure, the tested MKCs did not significantly affect the mortality rate of FAW (F = 0.7169; p = 0.6909) (Table 1). On the other hand, a clorantraniliprole-based insecticide used as a positive control promoted the total mortality of exposed FAW larvae. However, FAW larval weight was markedly reduced by the MKCs **4** and **5** (F = 3.6919; d.f. = 9, 50; p = 0.0013), while the remaining curcuminoids showed intermediate responses (Table 1).

Table 1: Means (±standard error) of mortality and larval weights of *Spodoptera frugiperda* larvae after seven days of exposure to artificial media containing the acetone-derived monoketone curcuminoids 1-8 (at 250 mg kg^{-1}) and a commercial insecticide based on chlorantraniliprole (Premio® 20 SC, positive control), which were tested at the recommended rate.

Treatments	Mortality (%)[1]	Larval weight (mg)[2]
1	6.94±2.56	196.67±48.69 abc
2	8.33±3.73	333.15±49.56 ab
3	2.78±1.76	335.45±44.06 ab
4	22.22±4.65	138.35±93.15 c
5	9.72±8.33	153.85±30.17 c
6	19.44±8.78	216.93±36.52 abc
7	22.92±6.25	295.05±27.04 abc
8	12.50±7.68	199.83±31.68 abc
Positive control	100.00±0.00*	—
Control (ethyl acetate)	4.17±1.86	320.81±55.25 abc
Control (water)	10.00±4.43	345.38±58.58 a
F	0.7169^{ns}	3.6919
d.f.	9, 50	9, 50
p-value	0.6909	0.0013

[1]Means followed by different letters in the columns indicate significant differences among treatments (GLM with quasibinomial distribution, followed by *post hoc* Tukey's test, $p<0.05$);
[2]Means followed by different letters in the columns indicate significant differences among treatments (GLM with Gaussian distribution, followed by *post hoc* Tukey's test, $p<0.05$);
*Not included in the statistical analysis (null variance).

In this study, the Claisen-Schmidt reaction was successfully employed in the synthesis of eight MKCs. The procedure proved to be a simple strategy to obtain MKCs with the following advantages: 1) the reaction time was 24 h at maximum; 2) the products were obtained by recrystallization, with yields varying from fair to excellent; 3) the versatility of this reaction allows the generation of a wide variety of MKCs from simple structural precursors.

Recently, the effects of curcumin derivatives on FAW in assays performed with Sf9 cells were reported (Kausar et al., 2024). Among the tested compounds, the pyrazole derivatives **IV** and **V**, and the guanidine-based derivative **VI** (Figure 2) displayed the highest percentage of cell growth inhibition at a concentration of 100 µM, surpassing the positive control *a*-mangostin. Based on these results, the authors investigated the insecticidal effects of compound **VII**, a monocarbonyl analog of curcumin, against *Bemisia tabaci* (Gennadius) (Hemiptera: Aleyrodidae) (Ioannou et al., 2025). Compound **VII** exhibited insecticidal activity associated with 71% inhibition of the CYP6CM1 enzyme, one of the main determinants of this insect's resistance to conventional insecticides, with an IC_{50} of 2.41 µM. Molecular docking studies with compound **VII** and **I** (curcumin) indicated that one of the catecholic/phenolic moieties stands close to the heme, while the second stands in distant regions of the binding site. In curcumin (**I**), the second aromatic end is stabilized through hydrophobicity with two phenylalanine residues, Phe193 and Phe471, and polar interactions of the hydroxyl and methoxy substituents with Glu294 and Ser470. In the case of compound VII, the interaction occurs via Ser95 and Thr100 and is further stabilized through hydrophobic interactions with Phe99. Therefore, the higher structural flexibility of compound **VII** compared to curcumin (**I**) due to a sp^3 carbon between the two carbonyl groups of curcumin's core is a critical factor underlying the differences in binding properties of compound **I** (curcumin) and **VII** (Ioannou et al., 2025). Although the individually tested compound showed low mortality, the combination of compound **VII** with imidacloprid raised mortality to 100%, highlighting the potential of these analogs as adjuvants in IPM strategies. The findings reported by Ioannou et al. (2025) led us to synthesize and investigate the larvicidal and growth inhibitory effects of eight MKCs (**1-8**) against FAW.

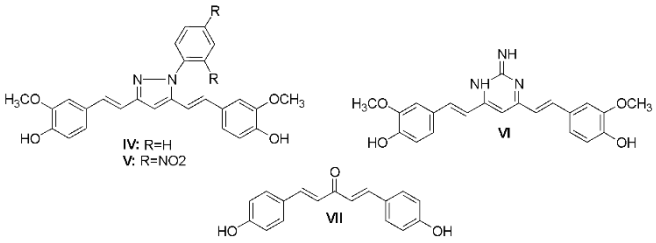


Figure 2. Chemical structures of compounds **IV-VII**.

According to the literature, larvicidal assays with mortality above 80% indicate strong activity, while values between 60 and 80% suggest moderate activity. Mortalities between 40 and 60% are indicative of weak activity, whereas values below 40% correspond to little or no activity (Gebissa et al., 2025). Regarding larval weight, there is no established criterion, but the results can be interpreted based on the percentage reduction compared to the control, complemented by statistical analyses that demonstrate significant differences in larval development. Based on these criteria, the results indicated that the synthesized compounds did not show a significant lethal toxicity on FAW, with all MKCs causing mortality below 25%. However,

compounds **4** and **5** stood out for promoting reductions of 59 and 55%, respectively, in the weight of FAW larvae in comparison to the negative control, indicating sublethal activity that compromises the initial development of the caterpillars.

The effects of compounds **4** and **5** on FAW larva are likely associated with reduced feeding activity and/or impaired digestive efficiency, resulting in lower nutrient assimilation. Additionally, the induction of detoxification enzymes, such as cytochrome P450 monooxygenases, may impose high metabolic costs, diverting energy from growth to maintenance processes (Ioannou et al., 2025). Such trade-offs are widely reported in herbivorous insects exposed to plant secondary metabolites (allelochemicals) and often result in delayed development and reduced biomass accumulation (Jeon et al., 2023; Ioannou et al., 2025). Similar sublethal effects have been documented for botanical compounds, including curcumin derivatives, which can negatively affect insect growth without causing immediate mortality (Jeon et al., 2023; Kausar et al., 2024; Ioannou et al., 2025).

Furthermore, MKCs **4** and **5** displayed fluorine and chlorine atoms in their structures, respectively. Modern agricultural insecticides are predominantly halogenated, with a prevalence of fluorinated, chlorinated, and mixed compounds, such as sulfoxaflor, cyantraniliprole, and flupyradifurone. The incorporation of halogens has been associated with increased potency, modulation of physicochemical properties, and greater metabolic stability, as well as enhanced penetration through biological barriers and reduced degradation by detoxification enzymes. In this context, broflanilide is a good example, as it shows high larvicidal activity against *Spodoptera litura* (Fabricius) (Lepidoptera: Noctuidae) and acts at a distinct site on the GABA-R receptor, including resistant populations (Jeschke, 2017). However, halogenation alone is not sufficient to ensure insecticidal activity; an underlying structure capable of supporting this activity is also required. Moreover, the results indicated that the nature of the halogen may play a key role in the larvicidal activity against FAW. Indeed, compound **6**, which displayed a bromine atom, was much less effective than MKCs **4** (R_3 = F) and **5** (R_3 = Cl) in decreasing the larval weight. On the other hand, compound **6** (R_3 = Br) caused an increased mortality percentage compared to MKC **4**. These differences might be associated with the different size, polarizability, and lipophilicity of these halogens and their different binding scores at specific receptor proteins of the insect. Bromine atoms are larger and more polarizable than fluorine, which increases their lipophilicity and helps compound **6** cross the insecticide cuticle more readily than **4** (Li et al., 2024; Xie et al., 2025). On the other hand, a chlorine atom has a better balance between steric bulk and polarizability compared to **6**, which causes a steady larval feeding cessation (Li et al., 2024; Xie et al., 2025). Differences between the efficacy of compounds containing different halogens in their structures on FAW were also reported for chalcones (Devi et al., 2021). Thus, the exploration of halogenated curcumin derivatives may represent a promising strategy for the development of new agricultural insecticides, especially when chlorine and fluorine substitution is combined with a molecular scaffold capable of sustaining biological activity.

CONCLUSION

The Claisen-Schmidt reaction proved to be an effective strategy for obtaining MKCs **1-8** with good yields, in addition to employing solvents of low environmental impact and simple setups. These aspects may facilitate the scale-up of this synthetic method. Among the MKCs evaluated, compounds **4** and **5** stood out for presenting relevant sublethal effects, mainly growth-inhibitory effects on FAW larvae. Taken together, these results indicate that the halogenation of monocarbonyl curcuminoids may be an interesting strategy for the development of molecules with larvicidal activity against lepidopteran pests of agricultural relevance and potential to be applied in IPM strategies. Further studies must address the synthesis of other halogenated MKCs derivatives bearing more halogens in the aromatic rings with different substitution patterns.

CONFLICT OF INTEREST

None to declare.

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