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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Chalcones as promising pesticidal agents against diamondback moth (*Plutella xylostella*): microwave-assisted synthesis and structure–activity relationship

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Abstract A series of chalcones (**A**–CH=CH–CO–**B**) were synthesized under microwave irradiation, and for the first time their pesticidal activity against diamondback moth (*Plutella xylostella*) was evaluated to identify the promising lead structures. The structure–activity relationship (SAR) analysis revealed that electron-withdrawing substituents on ring **A** of chalcone provided good pesticidal agents, whereas, ring **B** can bear either electron-withdrawing or electron-releasing substituents. Moreover, compound **22** having *para*-Cl substitution on ring **A** as well on ring **B** showed maximum activity with LC_{50} value of 170.24 μg mL^{-1}.

Keywords *Plutella xylostella* · Chalcones · Pesticidal · Structure–activity relationship · Microwave

Introduction

The diamondback moth, *Plutella xylostella* (L.) (Lepidoptera: Plutellidae), is one of the most destructive pests of crucifers worldwide (Talekar and Shelton, 1993; Verkerk and Wright, 1996). Larvae of *P. xylostella*, feed on the foliage of the cruciferous plants from the seedling stage to harvest and greatly reduce the yield and quality of produce. Control of *P. xylostella* has largely been dependent on use of various pesticides such as substituted hydrocarbons (Miyata *et al.*, 1986), carbamates (Miyata *et al.*, 1986), organophosphates (Miyata *et al.*, 1986), pyrethroids (Miyata *et al.*, 1986; Schuler *et al.*, 1998), benzophenyl ureas (Sun, 1990), emamectin benzoate (Zhao *et al.*, 2006), besides biopesticides such as *Bacillus thuringiensis* (Song, 1991; Sun, 1990; Tabashnik *et al.*, 1990). However, development of resistance for various classes of pesticides is a major concern for the effective management of this important crucifer defoliator (Miyata *et al.*, 1986; Talekar and Griggs, 1986; Sun, 1990; Tabashnik *et al.*, 1990; Song, 1991; Shelton *et al.*, 1993; Schuler *et al.*, 1998; Zhao *et al.*, 2006). On the other side, adverse effects of some of the above pesticides (Eskenazi *et al.*, 1999) to humans, animals, and environment besides difficulties associated with their preparations have fostered the need for developing new insect control agents with greater selectivity, better health, and environmental profiles.

Chalcones (1,3-diaryl-2-propen-1-ones) being structurally simple class of natural products have assumed importance because of their wide ranging biological profiles such as anti-inflammatory, antimalarial, antimicrobial, and anticancer activity (Nowakowska, 2007; Go *et al.*, 2005; Liu *et al.*, 2001; Dimmock *et al.*, 1999; Modzelewska *et al.*, 2006). On the other side, their synthesis with different substitution pattern on the two aryl rings (**A** and **B**) further allow exploring a large number of desired potential analogs. As a result, number of reports on the structure–activity relationship (SAR) of the substituted chalcones for various bioactivities still continue to appear in the literature including a recent study on antimalarial activity by our group (Kumar *et al.*, 2010). Moreover, insect antifeedant (Nalwar *et al.*, 2009), nematicidal (Awasthi *et al.*, 2009; Gonza′lez and Braun, 1998), and

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larvicidal (Das *et al.*, 2005; Begum *et al.*, 2010; Gautam and Chourasia, 2010) activities have also been shown by chalcone derivatives. However, to the best of our knowledge, pesticidal activity of chalcones against one of the most destructive crucifer defoliator, *P. xylostella* has not yet been explored.

In this study, for the first time, we have studied the pesticidal SAR of chalcones against *P. xylostella*, wherein, Cl substitution on ring **A** as well as on ring **B** of chalcone was found to be an important feature for good activity. All the chalcones were synthesized under microwave irradiation which offered several advantages over conventional techniques in terms of shorter reaction time, improvement in the yield, besides reduction in consumption of solvent (de la Hoz *et al.*, 2005).

Experimental

Materials and instruments

All the reagents/solvents were obtained from commercial sources (Merck or Sigma–Aldrich) and used without further purification. Column chromatography was performed using silica gel (60–120 mesh size). CEM Discover© focused microwave (2450 MHz, 300 W) was used for the synthesis of chalcone derivatives. ^{1}H (300 MHz) and ^{13}C (75.4 MHz) NMR spectra were recorded on a Bruker Avance-300 spectrometer using tetramethylsilane (TMS) as internal standard. HRMS-ESI spectra were determined using micromass Q-TOF ultima spectrometer.

Microwave-assisted synthesis of 4-(2,4,5-trimethoxyphenyl)but-3-en-2-one (**1**) from natural *β*-asarone of *Acorus calamus* oil (Scheme 1)

A mixture of *β*-asarone (0.31 g, 1.5 mmol), $NaIO_4$ (1.17 g, 5.5 mmol), OsO_4 (0.0004 g, 0.0015 mmol), and benzyltriethylammonium chloride (0.01 g, 0.04 mmol) were dissolved in H_2O–THF (3 mL, 4:1) and irradiated under focused microwave (150 W, 100°C) irradiation. After completion of the reaction, the mixture was extracted with ethyl acetate (3 × 15 mL) and vacuum evaporated to give a crude mixture, which on column chromatography with silica gel provided 2,4,5-trimethoxybenzaldehyde (Sinha *et al.*, 2003; Kumar *et al.*, 2010) in 83% yield. Subsequently, the above benzaldehyde (0.24 g, 1.22 mmol) was allowed to react with excess of acetone (3 mL) in the presence of ionic liquid 1-methyl-3-butanesulfonic acid imidazolium hydrogen sulfate ([MIMBSA]HSO_4) (1 g) under focused microwave irradiation (100 W, 75°C). The reaction mixture was vacuum evaporated and extracted with ethyl acetate (3 × 15 mL). The combined organic extract was washed with brine (2 × 5 mL), dried over sodium sulfate, and concentrated under reduced pressure. The obtained crude mixture was purified through column chromatography (silica gel 60–120 mesh size) and recrystallization with methanol to obtain the preferred pure product.

*4-(2,4,5-Trimethoxyphenyl)but-3-en-2-one (**1**)*

Deep yellow solid; yield 65%; m.p. 98–101°C. ^{1}H-NMR: (300 MHz, $CDCl_3$): 7.94 (1H, d, $J = 16.4$ Hz), 7.10 (1H, s), 6.69 (1H, d, $J = 16.4$ Hz), 6.56 (1H, s), 3.98 (3H, s), 3.94 (6H, s), and 2.42 (3H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 199.3, 154.4, 153.0, 143.9, 138.7, 125.7, 115.3, 110.8, 97.3, 56.9, 56.8, 56.5, and 27.4. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{13}H_{16}O_4$, calculated, 237.1121; observed, 237.1109.

*Synthesis of 4-(4-methoxyphenyl)but-3-en-2-one (**2**)*

Compound **2** was prepared from anethole (Scheme 1) employing a procedure similar to that described for compound **1.** Yellow solid; yield 61%; m.p. 67–71°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.48–7.42 (3H, m), 6.90 (2H, d, $J = 8.3$ Hz), 6.61 (1H, d, $J = 16.4$ Hz), 3.81 (3H, s), and 2.33 (3H, s); ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 198.1, 161.5, 143.1, 129.8, 127.0, 124.9, 114.3, 55.2, and 27.2.

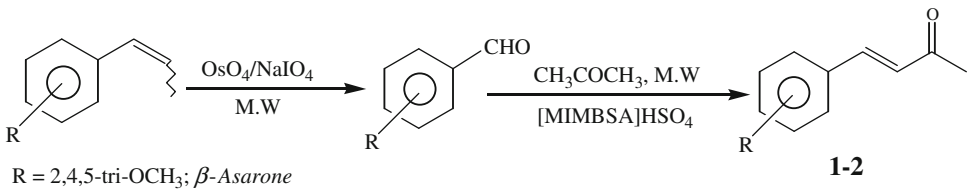
General procedure for microwave-assisted synthesis of chalcones (**4**–**24**) using aqueous NaOH as a condensing agent (Scheme 2)

Compounds **4**–**24** were prepared by Claisen-Schmidt condensation (Batovska *et al.*, 2009), wherein, equimolar amounts of acetophenone (3 mmol) and benzaldehyde (3 mmol) were taken in MeOH (5 mL). To this solution, 10% aqueous NaOH (6 mmol) was added, and the mixture was irradiated under focused microwave irradiation (110 W, 55°C) with continuous stirring for 20 min (or till completion of the reaction). The obtained precipitates were washed with dilute HCl, excess of water, methanol, dried in air, and finally recrystallized from methanol to obtain pure chalcones.

For comparison purpose, the above reactions were also accomplished at room temperature stirring where longer reaction time (3 h versus 20 min) besides large amount of solvent is required.

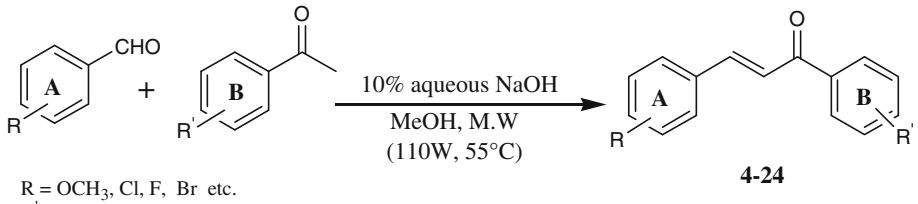
Compound **3** was prepared by Claisen-Schmidt condensation of 4-hydroxy-3-methoxybenzaldehyde (3 mmol) with excess of acetone (3 mL) using 10% aqueous NaOH (6 mmol) under microwave. The structures of synthesized chalcones (**3**–**24**) were confirmed by NMR spectral data as follows:

Scheme 1 Synthesis of chalcone derivatives **1** and **2** from natural phenylpropenes under microwave irradiation



R = 2,4,5-tri-OCH_3; *β-Asarone*
R = 4-OCH_3; *Anethole*

Scheme 2 Synthesis of chalcone derivatives **4–24** from substituted acetophenones and benzaldehydes under microwave irradiation



R = OCH_3, Cl, F, Br etc.
R' = OCH_3, CH_3, Cl, NO_2, OH, $OCH_2CH{=}CH_2$, OCH_2O etc.

*4-(4-Hydroxy-3-methoxyphenyl)but-3-en-2-one (**3**) (Sharma et al., 2006)*

Yellow solid; yield 56%; m.p.128–129°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.48 (1H, d, $J = 16.2$ Hz), 7.10–7.05 (2H, m), 6.94 (1H, d, $J = 8.2$ Hz), 6.61 (1H, d, $J = 16.2$ Hz), 3.92 (3H, s), and 2.37 (3H, s); ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 198.9, 148.7, 147.3, 144.2, 127.2, 125.3, 123.9, 115.2, 109.7, 56.3 and 27.6.

*1-(4-Nitrophenyl)-3-(thiophen-2-yl)prop-2-en-1-one (**4**)*

Yellow solid; yield 75%; m.p. 171–173°C. ^{1}H-NMR: (300 MHz, DMSO); 8.34–8.30 (4H, m), 7.99 (1H, d, $J = 15.0$ Hz), 7.83 (1H, s), 7.73 (1H, s), 7.57 (1H, d, $J = 15.0$ Hz), and 7.21 (1H, s); ^{13}C-NMR: (75.4 MHz, DMSO) 188.3, 150.2, 142.8, 139.9, 138.7, 134.2, 131.8, 130.2, 129.3, 124.3 and 120.5. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{13}H_9O_3NS$, calculated, 260.0376; observed, 260.0372.

*3-(Furan-2-yl)-1-(4-nitrophenyl)prop-2-en-1-one (**5**)*

Yellow solid; yield 79%; m.p. 139–142°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.27 (2H, d, $J = 8.4$ Hz), 8.09 (2H, d, $J = 8.8$ Hz), 7.58–7.49 (2H, m), 7.35 (1H, d, $J = 15.3$ Hz), 6.73 (1H, d, $J = 4.0$ Hz), and 6.48 (1H, s); ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.1, 151.2, 150.0, 145.6, 142.9, 132.1, 129.3, 123.8, 118.3, 117.7 and 113.0. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{13}H_9NO_4$, calculated, 244.0604; observed, 244.0615.

*1-(4-Methoxyphenyl)-3-(naphthalene-1-yl)prop-2-en-1-one (**6**) (Geyer et al., 2009)*

Yellow solid; yield 90%; m.p. 127–133°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.62 (1H, d, $J = 15.3$ Hz), 8.21 (1H, d, $J = 8.4$ Hz), 8.04 (2H, d, $J = 7.6$ Hz), 7.85–7.80 (3H, m), 7.59 (1H, d, $J = 15.3$ Hz), 7.51–7.42 (3H, m), 6.94 (2H, d, $J = 8.4$ Hz), and 3.81 (3H, s); ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.5, 163.5, 140.9, 133.7, 132.6, 131.8, 131.0, 130.9, 130.6, 128.7, 126.9, 126.3, 125.4, 125.0, 124.6, 123.6, 113.7, and 55.5.

*1,3-Bis(4-methoxyphenyl)prop-2-en-1-one (**7**) (Dong et al., 2008)*

Light yellow solid; yield 93%; m.p. 100–102°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.04 (2H, d, $J = 8.7$ Hz), 7.80 (1H, d, $J = 16.1$ Hz), 7.59 (2H, d, $J = 8.2$ Hz), 7.45 (1H, d, $J = 16.1$ Hz), 6.97–6.89 (4H, m), 3.84 (3H, s), and 3.81 (3H, s); ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.9, 163.5, 161.8, 144.0, 131.6, 130.9, 130.3, 128.1, 119.8, 114.6, 114.0, and 55.7.

*1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-en-1-one (**8**) (Liu et al., 2001)*

Creamy solid; yield 89%; m.p. 120–124°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.02–7.97 (2H, m), 7.86 (1H, d, $J = 16.6$ Hz), 7.66–7.62 (2H, m), 7.52–7.48 (2H, m), 7.44 (1H, d, $J = 16.6$ Hz), 7.00–6.96 (2H, m), and 3.89 (3H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 189.4, 162.2, 145.5, 139.3, 137.2, 130.7, 130.2, 129.2, 127.8, 119.5, 114.8, and 55.7.

*3-(4-Chlorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**9**) (Dong et al., 2008)*

Creamy solid; yield 88%; m.p. 128–131°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.97 (2H, d, $J = 9.2$ Hz), 7.69 (1H, d, $J = 16.1$ Hz), 7.50–7.41 (3H, m), 7.31 (2H, d, $J = 8.1$ Hz), 6.92 (2H, d, $J = 8.7$ Hz), and 3.81 (3H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.4, 163.5, 142.4, 136.1, 133.6, 130.8, 129.5, 129.2, 122.3, 113.9, and 55.5.

*3-(4-Fluorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**10**) (Liu et al., 2001)*

White solid; yield 93%; m.p. 115–118°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.07 (2H, d, $J = 8.8$ Hz), 7.81 (1H, d, $J = 15.6$ Hz), 7.67–7.63 (2H, m), 7.52 (1H, d, $J = 15.6$ Hz), 7.15–7.09 (2H, m), 7.01 (2H, d, $J = 8.1$ Hz), and 3.91 (3H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.6, 165.7, 163.6, 162.4, 142.7, 131.4, 130.9, 130.4, 121.7, 116.3, 116.0, 114.0, and 55.6. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{16}H_{13}O_2F$, calculated, 257.0972; observed, 257.0964.

*3-(4-Bromophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**11**)*

Off white solid; yield 91%; m.p. 149–152°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.34–8.28 (2H, m), 8.05–7.96 (1H, m), 7.80–7.52 (5H, m), 7.29–7.23 (2H, m), and 4.19 (3H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 189.2, 164.4, 143.3, 134.8, 133.0, 131.7, 130.5, 125.3, 123.2, 114.7, and 56.3. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{16}H_{13}BrO_2$, calculated, 317.0172; observed, 317.0172.

*1-(3,4-Dioxymethylene)-3-(4-chlorophenyl)prop-2-en-1-one (**12**)*

White solid; yield 87%; m.p. 164–167°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.68 (1H, d, $J = 15.7$ Hz), 7.57 (1H, d, $J = 8.0$ Hz), 7.49–7.44 (3H, m), 7.40 (1H, d, $J = 15.7$ Hz), 7.31 (2H, d, $J = 8.4$ Hz), 6.82 (1H, d, $J = 8.0$ Hz), and 5.98 (2H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 187.9, 151.8, 148.3, 142.7, 136.2, 133.5, 132.8, 129.5, 129.2, 124.7, 122.1, 108.4, 107.9, and 101.9. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{16}H_{11}ClO_3$, calculated, 287.0470; observed, 287.0469.

*3-(2,4-Dichlorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**13**)*

White solid; yield 88%; m.p. 134–137°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.09–8.00 (3H, m), 7.67 (1H, d, $J = 8.4$ Hz), 7.49 (1H, d, $J = 15.8$ Hz), 7.43 (1H, s), 7.28 (1H, d, $J = 8.4$ Hz), 6.98 (2H, d, $J = 8.2$ Hz), and 3.88 (3H, s); ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.4, 164.0, 138.6, 136.5, 136.2, 132.4, 131.3, 131.0, 130.4, 128.8, 127.8, 125.2, 114.3, and 55.8.

*3-(3,4-Dichlorophenyl)-1-(4-methoxyphenyl)prop-2-en-1-one (**14**)*

Pale yellow solid; yield 89%; m.p. 129–131°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.05 (2H, d, $J = 9.3$ Hz), 7.70–7.64 (2H, m), 7.54–7.42 (3H, m), 7.00 (2H, d, $J = 9.1$ Hz), and 3.90 (3H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.3, 164.0, 141.3, 135.6, 134.5, 133.6, 131.2, 131.1, 130.0, 127.8, 123.8, 114.3, and 55.9. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{16}H_{12}Cl_2O_2$, calculated, 307.0287; observed, 307.0280.

*3-(3,4-Dichlorophenyl)-1-(4-methylphenyl)prop-2-en-1-one (**15**)*

Light yellow solid; yield 86%; m.p. 137–138°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.95 (2H, d, $J = 6.9$ Hz), 7.71–7.65 (2H, m), 7.53–7.42 (3H, m), 7.32 (2H, d, $J = 7.1$ Hz), and 2.41 (3H, s), ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 189.5, 144.4, 141.7, 135.6, 135.5, 134.6, 133.6, 131.2, 130.1, 129.8, 129.0, 127.8, 123.9, and 22.0. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{16}H_{12}Cl_2O$, calculated, 291.0338; observed, 291.0335.

*3-(3,4-Dichlorophenyl)-1-(2-methoxyphenyl)prop-2-en-1-one (**16**)*

Yellow solid; yield 81%; m.p. 77–78°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.72–7.69 (2H, m), 7.62–7.33 (5H, m), 7.15–7.05 (2H, m), and 3.99 (3H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$); δ_C (75.4 MHz, $CDCl_3$) 192.4, 158.7, 140.2, 135.7, 134.3, 133.7, 133.5, 131.2, 130.9, 130.1, 129.2, 128.9, 127.7, 121.2, 112.1, and 56.2. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{16}H_{12}Cl_2O_2$, calculated, 307.0287; observed, 307.0284.

*3-(3,4-Dichlorophenyl)-1-(3-methoxyphenyl)prop-2-en-1-one (**17**)*

Light yellow solid; yield 79%; m.p. 105–107°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.80–7.74 (2H, m), 7.69 (1H, d, $J = 7.3$ Hz), 7.62–7.59 (2H, m), 7.56–7.47 (3H, m), 7.24 (1H, d, $J = 8.6$ Hz), and 3.97 (3H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 189.6, 160.1, 141.9, 139.2, 135.0, 134.5, 133.4, 131.0, 129.9, 129.8, 127.6, 123.6, 121.2, 119.7, 113.0, and 55.6. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{16}H_{12}Cl_2O_2$, calculated, 307.0287; observed, 307.0272.

*3-(3,4-Dichlorophenyl)-1-(3,4-dimethoxyphenyl)prop-2-en-1-one (**18**)*

White solid; yield 87%; m.p. 122–123°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.71–7.65 (3 H, m), 7.61 (1H, s), 7.55–7.45 (3H, m), 6.94 (1H, d, $J = 8.6$ Hz), and 3.97 (6H, s). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.3, 154.0, 149.8, 141.5, 135.6, 134.6, 133.7, 131.4, 130.1, 128.0, 123.7, 111.2, 110.5, 56.6, and 56.5. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{17}H_{14}Cl_2O_3$, calculated, 337.0393; observed, 337.0398.

*3-(3,4-Dichlorophenyl)-1-(3,4,5-trimethoxyphenyl)prop-2-en-1-one (**19**)*

Pale yellow solid; yield 83%; m.p. 139–140°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.72–7.67 (2H, m), 7.51–7.42 (3H, m), 7.20 (2H, s), and 3.95 (9H, s); ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.8, 153.6, 143.1, 142.2, 135.3, 134.7, 133.6, 133.4, 131.3, 130.1, 127.9, 123.5, 106.5, 61.4, and 56.8. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{18}H_{16}Cl_2O_4$, calculated, 367.0498; observed, 367.0493.

*1-(4-Chlorophenyl)-3-(3,4-dichlorophenyl)prop-2-en-1-one (**20**)*

Off white solid; yield 92%; m.p. 135–137°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.96–7.92 (2H, m), 7.70–7.63 (2H, m), and 7.48–7.40 (5H, m), ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.9, 142.8, 140.1, 136.6, 135.3, 135.1, 133.9, 131.5, 130.5, 130.3, 129.6, 128.1, and 123.4. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{15}H_9Cl_3O$, calculated, 310.9791; observed, 310.9786.

*1,3-Bis(3,4-dichlorophenyl)prop-2-en-1-one (**21**)*

Pale yellow solid; yield 88%; m.p. 164–167°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.10 (1H, s), 7.87–7.70 (3H, m), and 7.62–7.40 (4H, m); ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 187.7, 143.5, 138.1, 137.7, 135.2, 134.9, 133.8, 131.4, 131.2, 130.8, 130.3, 128.0, 127.9, and 122.7. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{15}H_8Cl_4O$, calculated, 344.9402; observed, 344.4444.

*1,3-Bis(4-chlorophenyl)prop-2-en-1-one (**22**) (Santos et al., 2006)*

Off white solid; yield 92%; m.p. 108–111°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 7.98 (2H, d, $J = 7.6$ Hz), 7.79 (1H, d, $J = 16.6$ Hz), 7.59 (2H, d, $J = 8.4$ Hz), and 7.50–7.39 (5H, m). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 189.1, 144.1, 139.7, 137.0, 136.7, 133.6, 130.2, 130.0, 129.7, 129.4, and 122.3.

*3-(4-Chlorophenyl)-1-(4-nitrophenyl)prop-2-en-1-one (**23**) (Batovska et al., 2009)*

Yellow solid; yield 73%; m.p. 158–161°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.37 (2H, d, $J = 7.2$ Hz), 8.16 (2H, d, $J = 7.2$ Hz), 7.82 (1H, d, $J = 15.6$ Hz), 7.61 (2H, d, $J = 8.2$ Hz), and 7.49–7.41 (3H, m). ^{13}C-NMR: (75.4 MHz, $CDCl_3$) 188.4, 149.8, 144.9, 142.5, 136.9, 132.5, 130.7, 129.1, 128.8, 123.6, and 121.4. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{15}H_{10}ClNO_3$, calculated, 288.0422; observed, 288.0425.

*3-(4-Chlorophenyl)-1-(4-hydroxyphenyl)prop-2-en-1-one (**24**) (Batovska et al., 2009)*

White solid; yield 54%; m.p. 178–179°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 9.31(1H, s), 8.10 (2H, s), 7.85–7.73 (4H, m), 7.48 (2H, s), and 6.98 (2H, s). ^{13}C-NMR: (75.4 MHz, CD_3COCD_3) 188.4, 163.4, 142.7, 136.7, 135.7, 132.5, 131.5, 130.4, 124.2, and 116.7.

Synthesis of 3-(4-chlorophenyl)-1-[4-(prop-2-en-1-yloxy)phenyl]prop-2-en-1-one (**25**)

To a 50-mL round bottom flask containing **24** (0.5 g, 1.9 mmol) in dry acetone (20 mL), allyl bromide (0.46 g, 3.8 mmol), and anhydrous K_2CO_3 (0.52 g, 3.8 mmol) were added. The mixture was refluxed for 6 h. After consumption of starting chalcone (monitored on TLC), the mixture was filtered to remove K_2CO_3. The filtrate was vacuum evaporated and washed with hexane to remove excess of allyl bromide. The obtained crude solid was recrystallized with methanol to afford the desired pure product.

Spectral data of the product **25**: White solid; yield 69%; m.p.119–120°C. ^{1}H-NMR: (300 MHz, $CDCl_3$); 8.05 (2H, d, $J = 8.0$ Hz), 7.77 (1H, d, $J = 16.2$ Hz), 7.58–7.49 (3H, m), 7.40 (2H, d, $J = 8.9$ Hz), 7.02 (2H, d, $J = 8.0$ Hz), 6.14–6.01 (1H, m), 5.48–5.31 (2H, m), and 4.64 (2H, d, $J = 5.1$ Hz); δ_C (75.4 MHz, $CDCl_3$) 188.7, 162.9, 142.7, 136.5, 134.0, 132.9, 131.4, 131.2, 129.8, 129.5, 122.7, 118.5, 115.0, and 69.3. HRMS-ESI: *m/z* $[M + H]^+$ for $C_{18}H_{15}ClO_2$, calculated, 299.0833; observed, 299.0833.

Biological evaluation

Test insect

Insects, *P. xylostella*, were obtained from infested field crops and reared in the laboratory. Adult insects were allowed to lay eggs on 1-week-old mustard plants grown in the pots and encaged inside the wooden boxes. Second instar larvae were removed from the mustard plants and transferred on to the cabbage leaves encaged in other boxes where the insect completed rest of the stages. The adults emerged from the pupae were allowed to lay eggs on the mustard plants placed in the cages. Insects were reared and maintained at 25 ± 1°C, 65 ± 5% RH and a photoperiod of 16:8 (L: D). Second instar larvae obtained from the established colony maintained for >20 generations in the laboratory were used in the experiments.

Bioassays for preliminary screening

The larvicidal activity of the test compounds (**1**–**25**) was evaluated by the leaf dip method against second instar

larvae. Larvicidal activity was evaluated on cabbage leaves ($\sim$34 cm^2). Known amounts of the test compounds was dissolved in acetone and then diluted with water to obtain a desired range of concentrations. The test compounds were suspended in distilled water using Triton X-100 LR spreader (s.d. Fine-Chem. Ltd; India) at 0.1 mL/L. Based on our previous experiences, (Tewary *et al.*, 2006) preliminary screening of the test compounds were carried out at two higher test dosages; 10000 μg mL^{-1} and 5000 μg mL^{-1}. Three leaf disks were separately dipped in each test solution for 30 s and allowed to dry at ambient conditions. Second instar larvae (10 larvae in each replicate), starved for 3–4 h, were transferred individually on treated and control (disks treated with water mixed with acetone: triton only) leaf disks placed in petri plates. Moistures build up inside the petri plates was swabbed after 24 h using tissue paper, and petri plates were resealed using parafilm. Mortality was determined at 48 h after larvae were placed on disks. Larvae, which did not show movements when probed with camel hairbrush, were considered dead. All the treated samples were maintained at 25 ± 1°C, 65 ± 5% RH and a photoperiod of 16:8 (L:D) in the laboratory.

Dose–response experiment

Based on the review of preliminary screening results, promising test compounds were selected and subjected to dose–response bioassay. Test compounds of six concentrations each were prepared to provide dosage in the range 1 mg/mL and set for bioassay as mentioned above. Commercial pesticide, deltamethrin, was estimated against *P. xylostella* as positive control. Seven concentrations (400, 200, 100, 50, 25, 12.5, and 6.25 μg mL^{-1}) of deltamethrin were prepared in the tap water by serial dilutions. For control set, leaf disks were treated with tap water only.

Statistical analysis

Mortality was corrected by using Abbott's formula (Abbott, 1925). Lethal concentration to kill 50% of the population relative to control values (LC_{50}) was determined using (EPA PROBIT ANALYSIS PROGRAM used for calculating LC/EC values version 1.5) (Finney, 1971).

Results and discussion

Our group has been working on the development of various green synthetic methodologies using microwave (Sharma *et al.*, 2009), ionic liquids (Kumar *et al.*, 2008) besides utilization of abundantly available natural precursors (Sinha *et al.*, 2003, Sinha *et al.*, 2007) for antimalarial and pesticidal activities (Kumar *et al.*, 2010; Bhardwaj *et al.*, 2010). In this study, initially we were interested in utilizing natural phenylpropenes (Ar–CH=CH–CH_3) for the synthesis of chalcone derivatives (Ar–CH=CH–CO–CH_3) using ionic liquid under microwave irradiation. Consequently, compounds **1** and **2** were prepared (Scheme 1) from natural *β*-asarone and anethole, respectively (Sinha *et al.*, 2003)**.** Chalcones **3–24** were prepared by Claisen-Schmidt condensation (Batovska *et al.*, 2009) between benzaldehydes and acetophenone (acetone in case of **3**) under microwave irradiation (Scheme 2)**.** Compound **25** was prepared by *O*-allylation of hydroxylated chalcone (**24**) with allyl bromide. All the synthesized chalcone derivatives (**1–25**) were tested against larvae of lepidopteron insect, *P. xylostella*. The % mortality and LC_{50} values (only for those compounds which showed 100% mortality at 5000 μg mL^{-1}) are presented in Tables 1 and 2.

Preliminary screening of compounds **1–7** (Table 1) for pesticidal activity did not show promising results (<30% mortality) against the larvae after 48 h of exposure time.

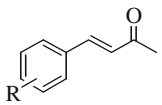
Moreover, the presence of an OH group in **3** and the naphthalene ring (**6**) created solubility problems.

In view of the well-known pesticidal potency of various chlorinated compounds, chalcone **8** having Cl substitution at ring **B** and OCH_3 at ring **A** was synthesized which showed 50% larval mortality at 10000 μg mL^{-1} dosage. To our surprise, reversal of the substituents (Cl v/s OCH_3) of **8** resulted in compound **9** with 100% mortality even at 5000 μg mL^{-1}. On the other side, replacement of Cl on ring **A** with F (**10**) or Br (**11**) substituents caused dramatic reduction in the larval mortality.

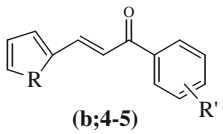
A comparison of the activities of compounds **7–12** indicates that electron-withdrawing substituents (particularly Cl) on ring **A** and electron-releasing substituents (particularly OCH_3) on ring **B** of chalcone (←A–CH=CH–CO–B←) increases the pesticidal potential while positional interchange (→B–CH=CH–CO–A→) of these substituents on both rings causes a decrease. Interestingly, above observation is in contrast to our recent finding (Kumar *et al.*, 2010) on antimalarial activity, wherein, potent chalcones were having electron-releasing substituents on ring **A** and electron-withdrawing substituents on ring **B**. Such findings would draw the attention of researchers in future while designing chalcone-based novel compounds with preferred activities.

Among the various tested chalcones (**1–12**, Table 1), compound **9** (LC_{50}: 356.45 μg mL^{-1}) was selected as prelude for further modification to improve and understand the pesticidal SARs. As expected, compounds with more electron-withdrawing substituents such as 2,4-dichloro (**13**, LC_{50}: 278.50 μg mL^{-1}) or 3,4-dichloro (**14**, LC_{50}: 287.64 μg mL^{-1}) on ring **A** exhibited better activity compared to single chloro (**9**, LC_{50}: 356.45 μg mL^{-1}).

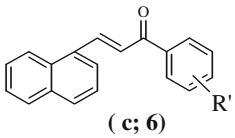
Table 1 Preliminary screening of chalcone derivatives against *P. xylostella* after 48 h



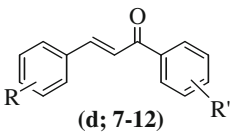
(a;1-3)



(b;4-5)



(c; 6)



(d; 7-12)

Compound	Type	R	R′	Mortality [%][a] ± SD		LC_{50} (μg mL^{-1})[b]
				10000 μg mL^{-1}	5000 μg mL^{-1}	
1	a	2,4,5-trimethoxy	–	26.6 ± 0.57	0 ± 0	–
2	a	4-methoxy	–	30 ± 0	26.6 ± 0.57	–
3	a	4-hydroxy-3-methoxy	–	Solubility problem	–	–
4	b	sulfur	4-nitro	30 ± 0	23.3 ± 0.57	–
5	b	oxygen	4-nitro	23 ± 0.57	16.6 ± 0.57	–
6	c	–	4-methoxy	Solubility problem	–	–
7	d	4-methoxy	4-methoxy	26.6 ± 0	16.6 ± 0.57	–
8	d	4-methoxy	4-chloro	50 ± 1.15	26.6 ± 0.57	–
9	d	4-chloro	4-methoxy	100 ± 0	100 ± 0	356.45
10	d	4-fluoro	4-methoxy	33.3 ± 0.57	26.6 ± 0.57	–
11	d	4-bromo	4-methoxy	10 ± 0	3.3 ± 0.57	–
12	d	4-chloro	3,4-methylenedioxy	23 ± 0	13.3 ± 0.57	–

[a] Data represent the mean values of the three replicates and mortality in control accounted using *Abbott's* formula

[b] Only for those compounds which showed 100% larval mortality at 5000 μg mL^{-1}

Although, pesticidal activities of both of the dichlorinated chalcones **13** and **14** (Table 2) are comparable; however, based on evaluation of dose–response data values, **14** could be a better candidate if 100% kill is considered on bioefficacy indicator parameter. Therefore, in further study, effect of different substituents on ring **B** in association with 3,4-dichloro substitution on ring **A** was evaluated (**15**–**21**, Table 2). Interestingly, replacement of OCH_3 group of compound **14** with another electron-releasing CH_3 group (**15**) induced less mortality.

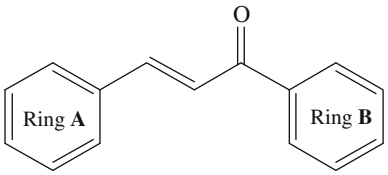
We next evaluated the positional importance of OCH_3 group on ring **B** for the activity. However, introduction of OCH_3 group at *meta* position (**17**) met with the solubility problem, whereas, its presence at *ortho* (**16**) position showed drastic reduction in the activity (see comparison between **14**, **16** and **17**, Table 2). Moreover, increase in the electron density on ring **B** with 3,4-dimethoxy (**18**) or 3,4,5-trimethoxy groups (**19**) provided lower activity as compared to **14**.

From a structure–activity perspective, effect of electron-withdrawing substituents on ring **B** was also evaluated. However, compounds **20** and **21** possessing 4-chloro and 3,4-dichloro substituents, respectively, were found inactive. A comparison of the % mortality of compounds **14**, **20** and **21** (Table 2) indicated that as we increased the number of Cl substituents from two to three or four, activity reduced significantly. Hence, it was realized that chalcone derivatives with two Cl substituents might increase the pesticidal potential.

Consequently, compound **22** possessing electron-withdrawing Cl substituent on ring **A** as well as on ring **B** was synthesized, and it showed good activity (**22**, LC_{50}: 170.24 μg mL^{-1}); however, introduction of polar NO_2 group (**23**) on ring **B** caused drastic reduction in the larval mortality. On the other side, replacement of Cl of **22** with isosteric polar group i.e., OH provided **24** (LC_{50}: 871.05 μg mL^{-1}) with lower activity. These results indicate the importance of both lipophilic as well as electron-withdrawing substitution (such as Cl) on ring **B** for enhanced pesticidal activity. The above assumption proved correct when **25** ($OCH_2CH{=}CH_2$; both lipophilic- and electron-releasing group) showed lesser activity than **22** but significantly improved activity than **24.** In the same vein, compound **9** (OCH_3 group) showed better activity than **24** (OH group) and marginally reduced activity than **25** ($OCH_2CH{=}CH_2$ group).

In order to develop dosages–response lines for the identified potent chalcones i.e., **9**, **13**, **14**, **22**, **24**, and **25**, their efficacy at different concentration were evaluated. LC_{50} values and other statistical parameters generated by linear regression analysis were compared and represented in Table 3. Overall pesticidal activity of the above potential chalcone was found to obey the following order: **22** > **25** > **13** > **14** > **9** > **24**.

Table 2 Pesticidal activity of chloro-substituted chalcones against *P. xylostella* after 48 h



Compound	Substitution on		Mortality [%][a] ± SD		LC_{50} (μg mL^{-1})[b]
	Ring **A**	Ring **B**	10000 μg mL^{-1}	5000 μg mL^{-1}	
13	2,4-dichloro	4-methoxy	100 ± 0	100 ± 0	278.50
14	3,4-dichloro	4-methoxy	100 ± 0	100 ± 0	287.64
15		4-methyl	83.3 ± 0.57	60 ± 0	–
16		2-methoxy	63.3 ± 0.57	50 ± 1	–
17		3-methoxy	Solubility problem	–	–
18		3,4-dimethoxy	68 ± 0.57	46.6 ± 0.57	–
19		3,4,5-trimethoxy	Solubility problem	–	–
20		4-chloro	97.7 ± 0	60 ± 0	–
21		3,4-dichloro	73.3 ± 0.57	46.6 ± 0.57	–
22	4-chloro	4-chloro	100 ± 0	100 ± 0	170.24
23		4-nitro	26.6 ± 0.57	20.0 ± 0	–
24[c]		4-hydroxy	100 ± 0	100 ± 0	871.05
25		4-allyl	100 ± 0	100 ± 0	268.20

[a] Data represent the mean values of the three replicates and mortality in control accounted using *Abbott's* formula

[b] Only for those compounds which showed 100% mortality at 5000 μg mL^{-1}

[c] Compounds **24** and **22** showed 100% mortality at 5000 μg mL^{-1}, whereas at lower concentration, compound **24** exhibited drastic reduction in the larval mortality as compared with **22**

Although, the identified potent compound **22** (LC_{50}: 170.24 μg mL^{-1}) is 27 times lesser active than the commercial pesticide deltamethrin (LC_{50}: 6.25 μg mL^{-1}), however, this study is the first report wherein a simple moiety like chalcone has provided a promising lead for pesticidal activity against *P. xylostella*. On the other hand, deltamethrin is known to leave residual traces in the environment which are quite harmful to humans (Villarini *et al.*, 1998), as compared with chalcones. Moreover, the identified potent chalcone **22** is reported to be a hypolipidemic agent (Santos *et al.*, 2006). Overall, this study will pave out a new platform for the development of chalcone-based economical pesticidal agents.

Proposed mode of action

A brief delving in the literature demonstrates the presence of glutathione *S*-transferase (GST) isoenzymes and GST

Table 3 Insecticidal activity (LC_{50} values and regression parameters of probit analysis) of the promising compounds against *P. xylostella* after 48 h

Serial no.	Compound no	LC_{50} values and regression parameters of probit analysis after 48 h				
		LC_{50} [FL] in μg mL^{-1}			χ^2	Intercept
		LC_{50}	Lower limit	Upper limit		
1	**9**	356.45	307.8	417.1	1.442	0.37623
2	**13**	278.50	213.2	367.8	6.682	0.07669
3	**14**	287.64	221.3	377.8	3.729	0.08344
4	**22**	170.24	130.2	222.08	1.644	1.91373
5	**24**	871.05	552.7	1950.8	1.477	1.33189
6	**25**	268.20	197.3	381.8	3.681	1.04128
7	Deltamethrin	6.25	2.21	11.9	4.189	4.02511

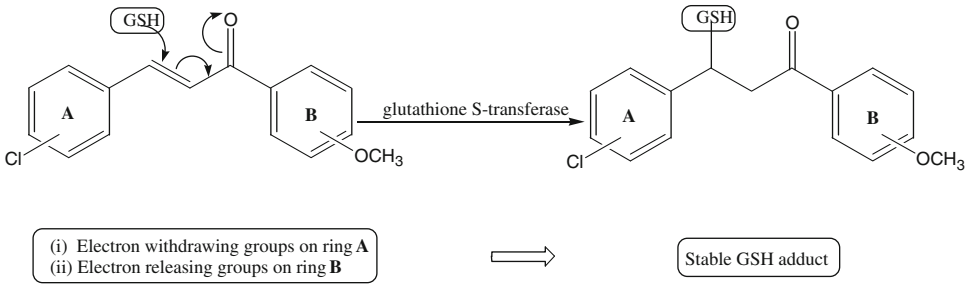


Fig. 1 Proposed Michael type addition of glutathione with chalcone

genes in *P. xylostella* which helps in detoxification of endogenous and xenobiotic compounds in vertebrates and invertebrates (Rushmore and Pickett, 1993; Sonoda *et al.*, 2006). Mode of action of chalcone may be attributed to the interaction of electrophilic β-position of α, β-unsaturated ketone bridge (–CH=CH–CO–), with reduced glutathione (GSH) to form its conjugate and consequent inhibition of GST (Miyamoto and Yamamoto, 1994). In general, electron-withdrawing groups on ring **A** and electron-releasing groups on ring **B** of chalcone would help increase the stability of GSH conjugate (Fig. 1) and therefore accounts for their pesticidal potential.

The above hypothesis demonstrates that compound **9** is more active than compound **8**. However, low activities of compounds **18** and **19** despite having more electron-releasing groups on ring **B** may be attributed to the reluctance of such chalcones toward Michael GSH adduct formation (Jin *et al.*, 2007). Besides electronic consideration, lipophilic, and hydrophilic characteristics of various substituents are also responsible for influencing the activity.

Conclusions

This study is the first report on the pesticidal potential of chalcones against *P. xylostella*, wherein, for good activity, electron-withdrawing ring **A** of chalcone was found crucial, while ring **B** can bear either electron-withdrawing or electron-releasing substituents. Particularly, Cl substitution and its positions on ring **A** as well as on ring **B** were found vital as compound 1,3-Bis(4-chlorophenyl)prop-2-en-1-one (**22**) showed the maximum activity with LC_{50} value of 170.24 μg mL^{-1}. The identified potent units can be further modified to exhibit better potency than commercial pesticides. In addition, the results of this study would be of value in guiding the design of novel chalcone-based pesticidal agents against *P. xylostella* and related insect pests.

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