Indian Journal of Chemistry
Vol. 65, August 2026, 754-762
DOI: 10.56042/ijc.v65i8.20679

Synthesis of 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]acetamides/acetohydrazides, 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-1-(piperidin-1-yl/morpholin-4-yl)ethan-1-ones, and related compounds as potential pesticides †

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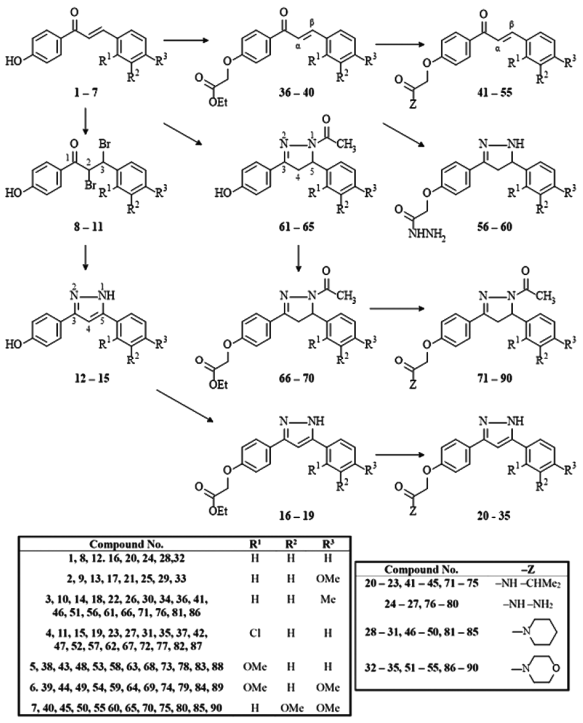
Received 17 June 2025; accepted (revised) 1 August 2026

The addition of bromine to (2*E*)-3-aryl-1-(4-hydroxyphenyl)prop-2-en-1-ones (**1**–**4**) produces the corresponding 3-aryl-2,3-dibromo-1-(4-hydroxyphenyl)propan-1-ones (**8**–**11**) that on treatment with hydrazine hydrate, yield 4-[5-aryl-1*H*-pyrazol-3-yl]phenols (**12**–**15**). Ethyl [4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]acetates (**16**–**19**), obtained by alkylation of **12**–**15** with ethyl chloroacetate, are further treated with propane-2-amine, hydrazine, piperidine, and morpholine to give the corresponding title compounds: 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-N-(propan-2-yl)acetamides (**20**–**23**), 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]acetohydrazides (**24**–**27**), 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-1-(piperidin-1-yl)ethan-1-ones (**28**–**31**), and 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-1-(morpholin-4-yl)ethan-1-ones (**32**–**35**). Alkylation of (2*E*)-3-aryl-1-(4-hydroxyphenyl)prop-2-en-1-ones (**3**–**7**) with ethyl chloroacetate gives ethyl [4-{(2*E*)-3-arylprop-2-enoyl}phenoxy]acetates (**36**–**40**) which on subsequent treatment with propan-2-amine, piperidine, and morpholine, produce 2-[4-{(2*E*)-3-arylprop-2-enoyl}phenoxy]-N-(propan-2-yl)acetamides (**41**–**45**), (2*E*)-3-aryl-1-[4-{2-oxo-2-(piperidin-1-yl)ethoxy}phenyl]prop-2-en-1-ones (**46**–**50**), and (2*E*)-3-aryl-1-[4-{2-(morpholin-4-yl)-2-oxoethoxy}phenyl]prop-2-en-1-ones (**51**–**55**) respectively. Treatment of **36**–**40** with hydrazine hydrate results in 2-[4-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetohydrazides (**56**–**60**). 1-[5-aryl-3-(4-hydroxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-ones (**61**–**65**), prepared by refluxing **3**–**7** with hydrazine hydrate, are alkylated with ethyl chloroacetate to yield ethyl [4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetates (**66**–**70**). These esters, when further treated with propane-2-amine, hydrazine, piperidine, and morpholine, produce the corresponding 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]-N-(propan-2-yl)acetamides (**71**–**75**), 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetohydrazides (**76**–**80**), 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]-1-(piperidin-1-yl)ethan-1-ones (**81**–**85**), and 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]-1-(morpholin-4-yl)ethan-1-ones (**86**–**90**).Some of these compounds exhibit promising growth inhibitory activity against phytopathogenic fungi, *Alternaria alternata*, *Fusarium solani*, and *Rhizoctonia solani*.

Keywords: Pyrazolylphenoxyacetamids, Pyrazolylphenoxyacetohydrazides, Piperidinylethanones, Morpholinylethanones, Antifungal Activity

Phytopathogenic fungi cause significant losses in the yield and quality of agricultural produce by infecting plant tissues at any of their growth stages both at pre- and post-harvest level[1,2]. Additionally, these fungi also produce mycotoxins that are harmful to both animal and human health[3-7].Therefore, effective control of fungal plant diseases is essential for agricultural production and food safety[8]. This is achieved by using fungicides of both natural and synthetic origin[9,10]. However, the continuous use of the same fungicide over time leads to the development of resistance in plant pathogens against these fungicides[11-13]. This necessitates the continuous synthesis of new compounds, that are likely to be used as fungicides, along with their primary *in vitro* screening to identify active compounds for further detailed studies. With these considerations and in continuation of our interest in the synthesis and evaluation of 4,5-dihydropyrazole derivatives[14-18], herein, we report our results on the synthesis and antifungal activity of title compounds: 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]acetamides, the corresponding acetohydrazides and 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-1-(piperidin-

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Compound No.	R^1	R^2	R^3
1, 8, 12. 16, 20, 24, 28,32	H	H	H
2, 9, 13, 17, 21, 25, 29, 33	H	H	OMe
3, 10, 14, 18, 22, 26, 30, 34, 36, 41, 46, 51, 56, 61, 66, 71, 76, 81, 86	H	H	Me
4, 11, 15, 19, 23, 27, 31, 35, 37, 42, 47, 52, 57, 62, 67, 72, 77, 82, 87	Cl	H	H
5, 38, 43, 48, 53, 58, 63, 68, 73, 78, 83, 88	OMe	H	H
6. 39, 44, 49, 54, 59, 64, 69, 74, 79, 84, 89	OMe	H	OMe
7, 40, 45, 50, 55 60, 65, 70, 75, 80, 85, 90	H	OMe	OMe

Compound No.	–Z
20 – 23, 41 – 45, 71 – 75	–NH –$CHMe_2$
24 – 27, 76 – 80	–NH –NH_2
28 – 31, 46 – 50, 81 – 85	
32 – 35, 51 – 55, 86 – 90	

Scheme 1 —Synthesis of substituted pyrazoles

1-yl/morpholin-4-yl)ethan-1-ones against some phytopathogenic fungi. The intermediate compounds were also used to synthesize some 2-[4-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetohydrazides, 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetamides, corresponding acetohydrazides, and 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]-1-(piperidin-1-yl/morpholin-4-yl)ethan-1-ones, and the results are included here.

Experimental Section

(2*E*)-3-aryl-1-(4-hydroxyphenyl)prop-2-en-1-ones (**1–7**, Scheme 1), required as starting materials, were available from our earlier studies or were prepared by the condensation of 4-hydroxyacetophenone with substituted araldehydes in 4% methanolic sodium hydroxide using similar procedures[15,16]. The homogeneity of the compounds was routinely checked by TLC on silica gel G using ethyl acetate : hexane (3 : 7) as the eluent. The melting points were determined on a "Ganson electric melting point apparatus" in open capillaries and are uncorrected. The IR spectra were recorded on a "Biorad FT-IR" spectrophotometer in KBr pallets, and frequencies are expressed in cm^{-1}. The ^{1}H NMR spectra were recorded on a "Bruker AM 300 (300 MHz)" instrument in deuterochloroform ($CDCl_3$), unless otherwise stated, using tetramethylsilane as an internal reference and chemical shifts are expressed in δ ppm units. The compounds were analyzed for C, H, and N on a "Carlo Erba Elemental Analyzer Model 1106" and the values were found within ±0.4% of the theoretical data. All compounds described here are named according to the latest IUPAC rules[19].

The compounds displayed expected IR and ^{1}H NMR spectral characteristics. However, only those spectral data, that have a direct bearing on structural assignments, are discussed here. The synthetic strategy adopted for the preparation of the compounds is outlined in Scheme 1, and their characterization data are given in Table 1. Methods of synthesis of representative compounds are described here and other related compounds were prepared from appropriate starting materials using similar methods.

2,3-Dibromo-1-(4-hydroxyphenyl)-3-(4-methylphenyl)propan-1-one, 10

A solution of bromine (3.20 g, 20 mmol) in chloroform 10 mL) was added drop-wise with constant stirring to a solution of **3** (4.76 g, 20 mmol) in chloroform (30 mL) at ice-cold temperature. Stirring was continued for an additional 30 minutes. The separated solid was filtered, washed with a small quantity of chloroform, and dried. The solid was purified by recrystallization from ethanol to give 6.76 g of **10**, yield 85%, m.p. 180°C. IR: 3369 (OH), 1662 (C=O); ^{1}H NMR: δ 2.39 (3H, s, C*H*$_3$), 5.63 (1H. d, C_3-*H*, *J* = 11 Hz), 5.85 (1H, d, C_2-*H*, *J* = 11 Hz), 6.97 (2H, d, *Arom H*, *o*- and *o'*- to OH, *J* = 9 Hz), 7.24 (2H, d, *Arom H*, *o*- and *o'*- to CH_3, *J* = 8 Hz), 7.43 (2H, d, *Arom H*, *m*- and *m'*- to CH_3, *J* = 8 Hz), 8.31 (2H, d, *Arom H*, *m*- and *m'*- to OH, *J* = 9 Hz). Anal. Calcd for $C_{16}H_{14}Br_2O_2$: C, 48.27; H, 3.54. Found: C, 47.99; H, 3.46%.

4-[5-(4-Methylphenyl)-1*H*-pyrazol-3-yl]phenol, 14

A mixture of **10** (3.98 g, 10 mmol), hydrazine hydrate (1.00 g 20 mmol, excess), and acetic acid (20 mL) was stirred for 24 hours. The reaction mixture was poured onto ice-water. The separated solid was filtered, washed with water, dried, and recrystallized from methanol to give 1.75 g of **14**, yield 70%, m.p. 147°C. IR: 3375 (OH, NH); ^{1}H NMR: δ 2.33 (3H, s, C*H*$_3$), 6.94 (2H, d, *Arom H*, *o*- and *o'*- to OH, *J* = 9 Hz), 7.22 (2H, d, *Arom H*, *o*- and *o'*- to CH_3, *J* = 8 Hz), 7.53 (2H, d, *Arom H*, *m*- and *m'*- to CH_3, *J* = 8 Hz), 8.08 (2H, d, *Arom H*, *m*- and *m'*- to OH, *J* = 9 Hz).

Anal. Calcd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.19. Found: C, 77.02; H, 5.46; N, 11.32%.

Ethyl [4-{5-(4-methoxyphenyl)-1*H*-pyrazol-3-yl}phenoxy]acetate, 18

A mixture of **14** (2.5 g, 10 mmol), ethyl chloroacetate (1.23 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol), and dimethylformamide (25 mL) was stirred for 24 hours. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was separated, washed with water several times, dried over anhydrous sodium sulfate, and concentrated. The residual gummy product was purified by column chromatography over silica gel using chloroform as eluant to give 2.52 g of **18**, yield 75% as a gummy solid. IR: 1755 (C=O of ester); ^{1}H NMR: δ 1.28 (3H, t, CH_2CH_3, J = 7 Hz), 2.34 (3H, s, CH_3), 4.29 (4H, q, CO_2CH_2, J = 7 Hz), 4.70 (2H, s, OCH_2CO_2), 6.91 (2H, d, *Arom H*, *o*- and *o'*- to OCH_2, J = 9 Hz), 7.04 (2H, d, *Arom H*, *o*- and *o'*- to CH_3, J = 8 Hz), 7.23 (2H, d, *Arom H*, *m*- and *m'*- to CH_3, J = 8 Hz), 7.95 (2H, d, *Arom H*, *m*- and *m'*- to OCH_2, J = 9 Hz). Anal. Calcd for $C_{20}H_{20}N_2O_3$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.08; H, 5.86; N, 8.48%.

2-[4-{5-(4-Methylphenyl)-1*H*-pyrazol-3-yl}phenoxy]-*N*-(propan-2-yl)acetamide, 22

A solution of **18** (1.68 g, 5 mmol) in propan-2-amine (5 mL, excess) was stirred for 48 hours. Propan-2-amine was removed by distillation and the residual product was purified by column chromatography over silica gel using ethyl acetate : hexane (1 : 5) as eluant to give 0.70 g of **22**, yield 40%, as a gummy solid. IR: 3310 (NH), 1660 (C=O); ^{1}H NMR: δ 1.25 (6H, d, $CH(CH_3)_2$, J = 7 Hz), 2.32 (3H, s, CH_3), 4.10 (1H, m, C*H*), 4.55 (2H, s, OCH_2), 7.02 (2H, d, *Arom H*, *o*- and *o'*- to OCH_2, J = 9 Hz), 7.08 (2H, d, *Arom H*, *o*- and *o'*- to CH_3, J = 8 Hz), 7.30 (2H, d, *Arom H*, *m*- and *m'*- to CH_3, J = 8 Hz), 7.99 (2H, d, *Arom H*, *m*- and *m'*- to OCH_2, J = 9 Hz). Anal. Calcd for $C_{21}H_{23}N_3O_2$: C, 72.18; H, 6.63; N, 12.03. Found: C, 71.88; H, 6.82; N, 11.86%.

2-[4-{5-(4-Methylphenyl)-1*H*-pyrazol-3-yl}phenoxy]acetohydrazide, 26

A solution of **18** (1.68 g, 5 mmol) and hydrazine hydrate 0.50 g (10 mmol) in ethanol was refluxed for one hour. The reaction mixture was diluted with ice-water, the separated solid was filtered, washed with water, dried, and recrystallized from methanol to give 0.93 g of **26**, yield 58%., m.p. 160°C. IR: 3314 (NH-NH_2), 1677 (C=O); ^{1}H NMR: δ 2.31 (3H, s, CH_3), 4.55 (2H, s, OCH_2). Anal. Calcd for $C_{18}H_{18}N_4O_2$: C, 67.07; H, 5.63; N, 17.38. Found: C, 66.88; H, 6.02; N, 17.36%.

2-[4-{5-(4-Methylphenyl)-1*H*-pyrazol-3-yl}phenoxy]-1-(piperidin-1-yl)ethan-1-one, 30

A solution of **18** (1.68g, 5 mmol) in piperidine (5 mL) was stirred for 48 hours. The reaction mixture was poured onto ice-water, the separated solid was filtered, washed with water, dried, and recrystallized from methanol to give 1.03 g of **30**, yield 55%, m.p. 180°C. IR: 3400 (NH), 1656 (C=O). Anal. Calcd for $C_{23}H_{25}N_3O_2$: C, 73.57; H, 6.71; N, 11.19. Found: C, 73.88; H, 6.41; N, 11.36%.

2-[4-{5-(4-Methylphenyl)-1*H*-pyrazol-3-yl}phenoxy]-1-(morpholin-4-yl)ethan-1-one, 34

A solution of **18** (1.68 g, 5 mmol) in morpholine (5 mL) was stirred for 48 hours. The reaction mixture was poured onto ice-water, the separated solid was filtered, washed with water, dried, and recrystallized from methanol to give 0.94 g of **34**, yield 50%, m.p. 195°C. IR: 3446 (NH), 1662 (C=O). Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 69.82; H, 6.48; N, 11.39%.

Ethyl [4-{(2*E*)-3-(4-methylphenyl)prop-2-enoyl}phenoxy]acetate, 36

A mixture of **3** (2.38 g, 10 mmol), ethyl chloroacetate (1.23 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol), and dimethylformamide (25 mL) was stirred for 24 hours. The reaction mixture was added to ice-cold water and extracted with ethyl acetate. The ethyl acetate extract was washed with water several times, dried over anhydrous sodium sulfate, and concentrated. The residual product was purified by column chromatography over silica gel using ethyl acetate : hexane (1 : 5) as eluant to give 2.69 g of **36**, yield 83%, m.p. 110°C. IR: 1758 (C=O of ester), 1655 (C=O); ^{1}H NMR: δ 1.26 (3H, t, CH_2CH_3, J = 7 Hz), 2.32 (3H, s, CH_3), 4.21 (2H, d, CO_2CH_2, J = 7 Hz), 4.70 (2H, s, OCH_2CO_2), 6.92 (2H, d, *Arom H*, *o*- and *o'*- to OCH_2, J = 8 Hz), 7.17 (2H, d, *Arom H*, *o*- and *o'*- to CH_3, J = 8 Hz), 7.56 (2H, d, *Arom H*, *m*- and *m'*- to CH_3, J = 8 Hz), 7.58 (1H, d, olefinic C_α-*H*, J = 16Hz), 7.70 (1H, d, olefinic C_β-H, J = 16 Hz), 8.03 (2H, d, *Arom H*, *m*- and *m'*- to OCH_2, J = 8 Hz). Anal. Calcd for $C_{20}H_{20}O_4$: C 74.06; H, 6.22. Found: C, 74.22; H, 6.05%.

(2*E*)-3-(4-Methylphenyl)-1-[4-{2-(morpholin-4-yl)-2-oxoethoxy}phenyl]prop-2-en-1-one, 51

A solution of **36** (0.32 g, 1 mmol) in morpholine (3 mL, excess) was stirred for 48 hours. The reaction mixture was poured onto ice-water. The separated solid was filtered, washed with water, dried, and recrystallized from methanol to give 0.31 g of **51**, yield 84%, m.p. 135°C. IR: 1673 (C=O of amide), 1659 (C=O, α,β unsaturated); ^{1}H NMR: δ 2.39 (3H, s, C*H*$_3$), 3.67 (8H, m, morpholinyl-*H*), 4.79 (2H, s, OC*H*$_2$CO$_2$), 7.03 (2H, d, *Arom H*, *o*- and *o'*- to OCH$_2$, *J* = 9 Hz), 7.22 (2H, d, *Arom H*, *o*- and *o'*- to CH$_3$, *J* = 8 Hz), 7.48 (1H, d, olefinic C$_\alpha$-*H*, *J* = 16 Hz), 7.54 (2H, d, *Arom H*, *m*- and *m'*- to CH$_3$, *J* = 8 Hz), 7.78 (1H, d, olefinic C$_\beta$-*H*, *J* = 16 Hz), 8.33 (2H, d, *Arom H*, *m*- and *m'*- to OCH$_2$, *J* = 9 Hz). Anal. Calcd for $C_{22}H_{23}NO_4$: C, 72.31; H, 6.34; N 3.83. Found: C, 72.54; H, 6.42; N, 3.91%.

2-[4-{5-(4-Methylphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl}phenoxy]acetohydrazide, 56

A solution of **36** (0.32 g, 1 mmol) and hydrazine hydrate (0.3 g, excess) in ethanol (5 mL) was refluxed for one hour. The reaction mixture was diluted with ice cold water. The separated solid was filtered, washed with water, dried, and recrystallized from ethanol to give 0.28 g of **56**, yield 86%, m.p. 208°C. IR: 3350, 3314 (NH-NH$_2$), 1681 (C=O of hydrazide); ^{1}H NMR (DMSO-d_6): δ 2.31 (3H, s, C*H*$_3$), 2.85 (1H, dd, *trans* C$_4$-*H*, *J* = 10 and 16 Hz), 3.37 (1H, dd, *cis* C$_4$-H, *J* = 11 and 16 Hz), 4.52 (2H, s, OC*H*$_2$), 4.81 (1H, dd, C$_5$-*H*, *J* = 10 and 11 Hz), 6.94 (2H, d, *Arom H*, *o*- and *o'*- to OCH$_2$, *J* = 9 Hz), 7.11 (2H, d, *Arom H*, *o*- and *o'*- to CH$_3$, *J* = 8 Hz), 7.25 (2H, d, *Arom H*, *m*- and *m'*- to CH$_3$, *J* = 8 Hz), 7.56 (2H, d, *Arom H*, *m*- and *m'*- to OCH$_2$, *J* = 9 Hz). Anal. Calcd for $C_{18}H_{20}N_4O_2$: C 66.65; H, 6.21; N, 17.27. Found: C, 66.27; H, 6.51; N, 17.43%.

1-[3-(4-Hydroxyphenyl)-5-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-one, 61

A mixture of **3** (2.38 g, 10 mmol), hydrazine hydrate (4 mL, excess), and acetic acid (20 mL) was refluxed for 8 hours. The reaction mixture was cooled and poured onto ice-water. The separated solid was filtered, washed with water, dried, and recrystallized from methanol to give 2.47 g of **61**, yield 84%, m.p. 254°C. IR: 3334 (OH), 1631 (C=O); ^{1}H NMR: δ 2.29 (3H, s, C*H*$_3$), 2.38 (3H, s, COC*H*$_3$), 3.08 (1H, dd, *trans* C$_4$-*H*, *J* = 4 and 18 Hz), 3.68 (1H, dd, *cis* C$_4$-*H*, *J* = 12 and 18 Hz), 5.50 (1H, dd, C$_5$-*H*, *J* = 4 and 12 Hz), 6.88 (2H, d, *Arom H*, *o*- and *o'*- to OH, *J* = 9 Hz), 7.10 (4H, s, *Arom H*, C$_5$-C$_6$*H*$_4$), 7.60 (2H, d, *Arom H*, *m*- and *m'*- to OH, *J* = 9 Hz). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C 73.45; H, 6.16; N, 9.52. Found: C, 73.58; H, 6.56; N, 9.84%.

Ethyl [4-{1-acetyl-5-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl}phenoxy]acetate, 66

A mixture of **61** (2.94 g, 10 mL), ethyl chloroacetate (1.23 g, 10 mmol), potassium carbonate (1.38 g, 10 mmol), and dimethylformamide (20 mL) was stirred for 24 hours. The reaction mixture was poured onto ice-water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sodium sulfate, and concentrated. The residual product was purified by chromatography over silica gel using ethyl acetate : hexane (1 : 4) as eluant to give 3.27 g of **66,** yield 86%, m.p. 110°C. ^{1}H NMR: δ 1.31 (3H, t, CH$_2$C*H*$_3$, *J* = 7 Hz), 2.29 (3H, s, C*H*$_3$), 2.40 (3H, s, COC*H*$_3$), 3.10 (1H, dd, *trans* C$_4$-*H*, *J* = 5 and 18 Hz), 3.68 (1H, dd, *cis* C$_4$-H, *J* = 12 and 18 Hz), 4.27 (2H, q, CO$_2$C*H*$_2$, *J* = 4 Hz), 4.64 (2H, s, OC*H*$_2$CO$_2$), 5.54 (1H, dd, C$_5$-*H*, *J* = 5 and 12 Hz), 6.94 (2H, d, *Arom H*, *o*- and *o'*- to OCH$_2$, *J* = 8 Hz), 7.10 (4H, s, *Arom H*, C$_5$-C$_6$*H*$_4$), 7.66 (2H, d, *Arom H*, *m*- and *m'*- to OCH$_2$, *J* = 8 Hz). Anal. Calcd for $C_{22}H_{24}N_2O_4$: C 69.46; H, 6.36; N, 7.36. Found: C, 69.66; H, 6.22; N, 7.59%.

2-[4-{1-Acetyl-5-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl}phenoxy]acetohydrazide, 76

A solution of **66** (0.38 g, 1 mmol) and hydrazine hydrate (0.1 g, 2 mmol) in ethanol was refluxed for one hour. The reaction mixture was cooled and diluted with ice-water. The separated solid was filtered, washed with water, dried, and recrystallized from methanol to give 0.31 g of **76**, yield 84%, m.p. 130°C. IR: 3314 (NHNH$_2$), 1656 (C=O); ^{1}H NMR: δ 2.30 (3H, s, *CH*$_3$), 2.35 (3H, s, C*H*$_3$), 3.08 (lH, dd, *trans* C$_4$-*H*, *J* = 4 and 18 Hz), 3.74 (1H, dd, *cis* C$_4$-*H*, *J* = 12 and 18 Hz), 4.56 (2H, s, OC*H*$_2$), 5.50 (lH dd, C$_5$-*H*, J=4 and 12 Hz). Anal. Calcd for $C_{20}H_{22}N_4O_3$: C 65.56; H 6.05; N 15.29. Found: C, 65.62; H, 6.24; N, 15.00%.

2-[4-{1-Acetyl-5-(4-methylphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl}phenoxy]-1-(morpholin-4-yl)ethan-1-one, 86

A solution of **66** (0.38 g, 1 mmol) in morpholine 3 mL was stirred for 48 hours. The reaction mixture

was diluted with water and extracted with ethyl acetate. The extract was washed with water, dried over anhydrous sulfate, and concentrated. The residual oil was purified by column chromatography over silica gel using ethyl acetate : hexane (1 : 5) as eluant to give 0.37 g of **86**, yield 88%, m.p. 140°C. ^{1}H NMR: δ 2.29 (3H, s, C*H*$_3$), 2.39 (3H, s, COC*H*$_3$), 3.10 (1H, dd, *trans* C$_4$-*H*, *J* = 4 and 18 Hz), 3.65 (9H, m, morpholinyl-H and *cis* C$_4$-*H*), 4.74 (2H, s, OC*H*$_2$CO$_2$), 5.54 (1H, dd, C$_5$-*H*, *J* = 4 and 12 Hz), 6.96 (2H, d, *Arom H*, *o*- and *o'*- to OCH$_2$, *J* = 8 Hz), 7.11 (4H, s, *Arom H*, C$_5$-C$_6$*H*$_4$), 7.67 (2H, d, *Arom H*, *m*- and *m'*- to OCH$_2$, *J* = 8 Hz). Anal. Calcd for $C_{24}H_{27}N_3O_4$: C 68.39; H, 6.46; N, 9.97. Found: C, 68.62; H, 6.14; N, 10.12%.

Results and Discussion

Addition of bromine to (2*E*)-3-aryl-1-(4-hydroxyphenyl)phenylprop-2-en-1-ones (**1–4)** furnished the corresponding 3-aryl-2,3-dibromo-1-(4-hydroxyphenyl)propan-1-ones (**8–11)** in good yields. In these reactions, the probability of electrophilic substitution in aromatic rings is excluded since in the ^{1}H NMR spectra of the products all aromatic protons appeared at their expected chemical shifts. Furthermore, the proton C$_2$-*H* appeared downfield compared to C$_3$-*H* as AB doublets with expected J values of 11 Hz. As an example, in compound **10**, C$_2$-*H* and C$_3$-*H* appeared at δ 5.85 and δ 5.63 respectively with *J* = 11 Hz. These results are in conformity with those reported earlier[20-22].

Treatment of **8–11** with hydrazine hydrate in glacial acetic acid at RT gave 4-[5-aryl-1*H*-pyrazol-3-yl]phenols (**12–15**) respectively in respectable yields. Alkylation of **12–15** with ethyl chloroacetate in the presence of anhydrous potassium carbonate in dimethylformamide at RT gave the corresponding ethyl [4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]acetates (**16–19**) in good yields. The formation of the compounds with proposed structure was confirmed by the appearance of a triplet and a quartet for ethyl and a singlet for OC*H*$_2$ protons in their ^{1}H NMR spectra. As an example, the triplet for C*H*$_3$ and quartet for C*H*$_2$ at δ 1.28 and δ 4.29 respectively both with *J* = 7 Hz were observed in the ^{1}H NMR spectrum of **18**. A singlet for OC*H*$_2$CO was displayed at δ 4.70. Absorption at 1755 cm^{-1} in its IR spectrum for C=O of ester further confirmed the proposed structure.

Acylation of propan-2-amine, piperidine and morpholine with the esters **16–19** at RT furnished the corresponding title compounds: 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-N-(propan-2-yl)acetamides (**20–23**), 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-1-(piperidin-1-yl)ethan-1-ones (**28–31**), and 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-1-(morpholin-4-yl)ethan-1-ones (**32–35**). The acetohydrazides, 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]acetohydrazides (**24–27**), were prepared by refluxing of esters **16–19** with hydrazine hydrate in ethanol.

Alkylation of (2*E*)-3-aryl-1-(4-hydroxyphenyl)prop-2-en-1-ones (**3–7**) with ethyl chloroacetate in the presence of anhydrous potassium carbonate in dimethylformamide at RT gave the corresponding ethyl [4-{(2*E*)-3-arylprop-2-enoyl}phenoxy]acetates (**36–40**). The two olefinic hydrogens, C$_\alpha$-*H* and C$_\beta$-*H*, appeared as two AB doublets with $J_{\alpha\beta}$ = 16 Hz in their ^{1}H NMR spectra indicating their *E*-configuration around the olefinic double bond in these compounds. Treatment of esters **36–40** with propan-2-amine, piperidine and morpholine gave 2-[4-{(2*E*)-3-arylprop-2-enoyl}phenoxy]-N-(propan-2-yl)acetamides (**41–45**), (2*E*)-3-aryl-1-[4-{2-oxo-2-(piperidin-1-yl)ethoxy}-phenyl]prop-2-en-1-one (**46–50**), and (2*E*)-3-aryl-1-[4-{2-(morpholin-4-yl)-2-oxoethoxy}-phenyl]aryl-prop-2-en-1-ones (**51–55**) respectively. These compounds were also assigned *E*-configuration based on $J_{\alpha\beta}$ = 16 Hz for AB doublets for olefinic hydrogens in their ^{1}H NMR spectra.

Treatment of esters **36–40** with hydrazine hydrate leads simultaneously to hydrazinolysis of its ester function and addition of hydrazine to its α,β-unsaturated keto function leading to 2-[4-(5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetohydrazides (**56–60**). Refluxing of **3–7** with hydrazine hydrate in glacial acetic acid gave 1-[5-aryl-3-(4-hydroxyphenyl)-4,5-dihydro-1*H*-pyrazol-1-yl]ethan-1-ones (**61–65**) in excellent yields. Treatment of **61–65** with ethyl chloroacetate in presence of anhydrous potassium carbonate in dimethyl formamide at RT gave the corresponding ethyl [4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetates (**66–70**) in good yields. The compounds displayed characteristic ^{1}H NMR spectra. The geminal protons at C-4, that are adjacent to the chiral center at C-5, showed magnetic non-equivalence and, therefore, appeared at different chemical shifts as ABX pattern of three doublets of doublets. The C$_4$-*H trans* to C$_5$-*H*, resonated at a higher field as compared to *cis* C$_4$-*H*. Also, the *trans* C$_4$-*H* showed a much lower value of coupling constant (5 Hz) with C$_5$-*H* than that shown by the *cis* C$_4$-*H* (12 Hz). All these results are in conformity with

the results reported previously from this laboratory[15-18, 23,24] and elsewhere[25-27]. Usual acylation of propan-2-amine, hydrazine hydrate, piperidine and morpholine with esters **66–70** gave title compounds, 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]-N-(propan-2-yl)acetamides (**71–75),** 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetohydrazides (**76–80**), 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]-1-(piperidin-1-yl)ethan-1-ones (**81–85**), and 2-[4-(1-acetyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]-1-(morpholin-4-yl)ethan-1-ones (**86–90**), respectively.

The compounds were identified by their characteristic IR and ^{1}H NMR spectra and elemental analysis.

Antifungal activity

The compounds were screened for their *in vitro* growth-inhibitory activity against three phytopathogenic fungi namely *Alternaria alternata, Fusarium solani* and *Rhizoctonia solani*. The cultures were maintained on Czapek's Dox agar slants[28] at 5°C. A standard fungicide, carbendazim (2-methoxycarbamoylbenzimidazole) was also tested under similar conditions for comparison. Stock solutions of the compounds and standard fungicide at a concentration of 1 mg mL^{-1} were prepared in dimethylsulfoxide. The activity of the compounds against the fungi was carried out using two-fold serial-dilution technique[29] at different concentrations of 100, 50, 25, 12.5, 6.25 and 3.13 μg mL^{-1} concentrations. The results are recorded as minimum inhibitory concentration (MIC, μg mL^{-1}) at which the test compound inhibited the growth of test organism and results are presented in Table 1.

A perusal of the data in Table 1 shows that many of the compounds inhibited the growth of the tested fungi at varying concentrations. In general, the pyrazole derivatives were more active than their corresponding 4,5-dihydropyrazole derivatives.

The compounds showed higher growth inhibitory activity against *A. alternata* than against the other fungi. The most active compound was found to be **17** which inhibited the growth of *A. alternata* at a concentration of 3.13 μg mL^{-1}. The compounds **8**, **13** and **16** were active at 6.25 μg mL^{-1}, whereas

Table 1 — Characterization data and growth inhibitory activity of title and intermediate compounds

Compd [a]	Mol. Formula	Yield (%)	m.p. (°C)	Minimum Inhibitory Concentration (MIC) μg mL^{-1} against [b]		
				A. alternata	*F. solani*	*R. solani*
8	$C_{15}H_{12}Br_2O_2$	83	165	6.25	25	12.5
9	$C_{16}H_{14}Br_2O_3$	80	175	50	50	50
10	$C_{16}H_{14}Br_2O_2$	85	180	25	12.5	50
11	$C_{15}H_{11}Br_2ClO_2$	75	120	12.5	50	25
12	$C_{15}H_{12}N_2O$	68	155	25	12.5	6.25
13	$C_{16}H_{14}N_2O_2$	60	174	6.25	50	–
14	$C_{16}H_{14}N_2O$	70	147	50	50	100
15	$C_{15}H_{11}ClN_2O$	70	135	50	50	50
16	$C_{19}H_{18}N_2O_3$	63	Gum	6.25	25	25
17	$C_{20}H_{20}N_2O_4$	70	Gum	3.13	50	50
18	$C_{20}H_{20}N_2O_3$	75	Gum	25	50	–
19	$C_{19}H_{17}ClN_2O_3$	65	Gum	25	50	50
20	$C_{20}H_{21}N_3O_2$	45	Gum	25	50	50
21	$C_{21}H_{23}N_3O_3$	35	Gum	25	25	50
22	$C_{21}H_{23}N_3O_2$	40	Gum	50	50	100
23	$C_{20}H_{20}ClN_3O_2$	43	Gum	50	50	100
24	$C_{17}H_{16}N_4O_2$	70	170	25	12.5	50
25	$C_{18}H_{18}N_4O_3$	82	210	50	50	25
26	$C_{18}H_{18}N_4O_2$	58	160	100	50	50
27	$C_{17}H_{15}ClN_4O_2$	78	180	50	100	100
28	$C_{22}H_{23}N_3O_2$	53	160	25	50	50
29	$C_{23}H_{25}N_3O_3$	65	200	12.5	50	50
30	$C_{23}H_{25}N_3O_2$	55	180	50	50	100
31	$C_{22}H_{22}ClN_3O_2$	45	Gum	50	100	100

(Contd.)

Table 1 — Characterization data and growth inhibitory activity of title and intermediate compounds *(Contd.)*

Compd [a]	Mol. Formula	Yield (%)	m.p. (°C)	Minimum Inhibitory Concentration (MIC) μg mL^{-1} against [b]		
				A. alternata	*F. solani*	*R. solani*
32	$C_{21}H_{21}N_3O_3$	60	Gum	25	50	50
33	$C_{22}H_{23}N_3O_4$	72	182	50	50	50
34	$C_{22}H_{23}N_3O_3$	50	195	50	50	50
35	$C_{21}H_{20}ClN_3O_3$	53	Gum	100	100	100
36	$C_{20}H_{20}O_4$	83	110	25	–	–
37	$C_{19}H_{17}ClO_4$	70	100	25	50	–
38	$C_{20}H_{20}O_5$	72	Gum	50	50	–
39	$C_{21}H_{22}O_6$	70	100	25	50	50
40	$C_{21}H_{22}O_6$	68	111	100	100	–
41	$C_{21}H_{23}NO_3$	85	155	100	–	–
42	$C_{20}H_{20}ClNO_3$	65	185	100	100	100
43	$C_{21}H_{23}NO_4$	65	155	–	–	–
44	$C_{22}H_{25}NO_5$	60	135	–	–	–
45	$C_{22}H_{25}NO_5$	65	140	–	–	–
46	$C_{23}H_{25}NO_3$	64	Gum	50	50	50
47	$C_{22}H_{22}ClNO_3$	58	245	50	50	50
48	$C_{23}H_{25}NO_4$	60	Gum	–	–	–
49	$C_{24}H_{27}NO_5$	45	180	–	–	–
50	$C_{24}H_{27}NO_5$	50	153	–	–	–
51	$C_{22}H_{23}NO_4$	84	135	100	–	–
52	$C_{21}H_{20}ClNO_4$	64	110	–	–	–
53	$C_{22}H_{23}NO_5$	66	178	50	50	50
54	$C_{23}H_{25}NO_6$	52	210	–	–	–
55	$C_{23}H_{25}NO_6$	70	143	–	–	–
56	$C_{18}H_{20}N_4O_2$	86	208	50	–	–
57	$C_{17}H_{17}ClN_4O_2$	68	170	–	–	–
58	$C_{18}H_{20}N_4O_3$	66	145	–	–	–
59	$C_{19}H_{22}N_4O_4$	60	155	50	100	50
60	$C_{19}H_{22}N_4O_4$	48	160	–	–	–
61	$C_{18}H_{18}N_2O_2$	84	254	50	100	–
62	$C_{17}H_{15}ClN_2O_2$	68	200	50	50	50
63	$C_{18}H_{18}N_2O_3$	65	185	12.5	50	100
64	$C_{19}H_{20}N_2O_4$	57	Gum	–	–	–
65	$C_{19}H_{20}N_2O_4$	60	90	–	–	–
66	$C_{22}H_{24}N_2O_4$	86	110	100	100	–
67	$C_{21}H_{21}ClN_2O_4$	68	170	100	50	50
68	$C_{22}H_{24}N_2O_5$	75	108	25	50	50
69	$C_{23}H_{26}N_2O_6$	80	Gum	100	100	100
70	$C_{23}H_{26}N_2O_6$	78	Gum	–	–	–
71	$C_{23}H_{27}N_3O_3$	74	Gum	100	50	–
72	$C_{22}H_{24}ClN_3O_3$	50	120	–	–	–
73	$C_{23}H_{27}N_3O_4$	60	130	100	100	100
74	$C_{24}H_{29}N_3O_5$	56	gum	100	100	50
75	$C_{24}H_{29}N_3O_5$	50	Gum	50	100	50
76	$C_{20}H_{22}N_4O_3$	84	130	50	25	–
77	$C_{19}H_{19}ClN_4O_3$	45	128	100	–	–
78	$C_{20}H_{22}N_4O_4$	50	140	100	–	–
79	$C_{21}H_{24}N_4O_5$	58	210	–	100	50
80	$C_{21}H_{24}N_4O_5$	60	155	100	–	–
81	$C_{25}H_{29}N_3O_3$	53	Gum	50	50	50
82	$C_{24}H_{26}ClN_3O_3$	70	115	–	–	–
83	$C_{25}H_{29}N_3O_4$	45	165	100	100	50

(Contd.)

Table 1 — Characterization data and growth inhibitory activity of title and intermediate compounds *(Contd.)*

Compd [a]	Mol. Formula	Yield (%)	m.p. (°C)	Minimum Inhibitory Concentration (MIC) μg mL^{-1} against [b]		
				A. alternata	*F. solani*	*R. solani*
84	$C_{26}H_{31}N_3O_5$	48	80	–	100	–
85	$C_{26}H_{31}N_3O_5$	30	Gum	–	–	–
86	$C_{24}H_{27}N_3O_4$	88	140	100	50	–
87	$C_{23}H_{24}ClN_3O_4$	40	105	–	–	–
88	$C_{24}H_{27}N_3O_5$	53	80	100	100	–
89	$C_{25}H_{29}N_3O_6$	52	95	–	–	50
90	$C_{25}H_{29}N_3O_6$	48	100	100	–	100

[a] Compound no.'s described here refer to those given in Scheme 1. [b] Dash "–" indicates that the test compound did not inhibit the growth of the test fungi up to a concentration of 100 μg mL^{-1}.

compounds **11**, **29** and **63** showed activity at 12.5 μg mL^{-1}. Many other compounds as shown in Table 1 were effective at different concentrations of 25 – 100 μg mL^{-1}. The growth of *F. solani* was inhibited by **10**, **12** and **24** at a concentration of 12.5 μg mL^{-1}. Many other compounds were active at 25 – 100 μg mL^{-1} against this fungus (Table 1). The compound **12** was effective against *R. solani* at a concentration of 6.25 μg mL^{-1} whereas the other compounds **8** was active at 12.5 μg mL^{-1}.

None of the compound surpassed the activity of standard fungicide, carbendazim, which was active against all fungi tested at lowest tested concentration of 3.13 μg mL^{-1}. Although, the structure activity relationship could not be drawn due to mixed pattern of activity exhibited by these compounds, but some of the compounds that showed activity at lower concentrations provide an opportunity to improve upon their activity by further structural modifications.

Conclusions

Several 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-acetamides, 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-acetohydrazides, 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]- 1-(piperidin-1-yl)ethan-1-ones, and 2-[4-(5-aryl-1*H*-pyrazol-3-yl)phenoxy]-1-(morpholin-4-yl)-ethan-1-ones along with some related 4,5-dihydro-1*H*-pyrazole derivatives were synthesized. The compounds were characterized by IR and ^{1}H NMR spectra and corroborated with their microanalytical data. Some of the compounds showed promising antifungal activity against phytopathogenic fungi which are likely to provide structural leads for improvement in their activity by further structural modifications.

Acknowledgements

Instrumental facilities provided by Regional Sophisticated Instrumentation Centre (now renamed Sophisticated Analytical Instrumentation Facility), Punjab University, Chandigarh are gratefully acknowledged.

References

1 Savary S, Willocquet L, Pethybridge S J, Eskar P M, Roberts N & Nelson A, *Nat Ecol Evol,* 3 (2019) 430.
2 Savary S, Teng P S, Willocquet L & Nutter F W J, *Annu Rev Phytopathol*, 44 (2006) 89.
3 Bräse S, Encinas A, Keck J & Nising C F, *Chem Rev*, 109 (2009) 3903.
4 Chen Y, Kistler H C & Ma Z, *Annu Rev Phytopathol,* 57 (2019) 15.
5 Janik E, Niemcewicz M, Ceremuga M, Stela M, Saluk-Bijak J, Siadkowski A & Bijak M, *Int J Mol Sci*, 21 (2020) 8187.
6 Khan R, Anwarb F & Ghazali F M, *Heliyon*, 10 (2024) e28361.
7 Omotayo1 O P, Omotayo A O, Mwanza M & Babalola O O, *Toxico Res,* 35 (2019) 1.
8 Stukenbrock E & Gurr S, *Nature*, 617 (2023) 31.
9 Brauer V S, Rezende C P, Pessoni A M, De Paula R G, Rangappa K S, Nayaka S C, Gupta V K & Almeida F, *Biomolecules*, 9 (2019) 521.
10 Sbai H, Hajib A, Msairi S, Amalich S, Bouyahya A, Lee L-H, Goh K W, Tabyaoui M & Harhar H, *J Agric Food Res*, 18 (2024) 101447.
11 Delp C J, *Plant Dis*, 64 (1980) 652.
12 Zubrod J P, Bundschuh M, Arts G, Brühl C A, Imfeld G, Knäbel A, Payraudeau S, Rasmussen J J, Rohr J, Scharmüller A, Smalling K, Stehle S, Schulz R & Schäfer R B, *Environ. Sci. Technol*, 53 (2019) 3347.
13 Yin, Y, Mioa J, Shao W, Liu X, Zhao Y & Ma Z, *Phytopathology*, 113 (2023) 707.
14 Dubey A K & Sangwan N K, *Indian J Chem,* 33B (1994) 1043.
15 Malik H, Dahiya A, Kumar R, Sangwan M S, Mehta N & Sangwan N K, *Indian J Chem*, 40B (2001) 682.
16 Malik H, Kaur P, Dahiya A & Sangwan N K, *Indian J Chem*, 63 (2024) 137.
17 Saini C & Sangwan N K, *Indian J Chem*, 61 (2022) 1257.
18 Sangwan N K, Verma B S & Dhindsa K S, *Indian J Chem*, 31 (1992) 590.
19 Favre H A & Powell W H, *Nomenclature of Organic Chemistry,* (RSC Publishing), 2013. https://doi.org/10.1039/9781849733069.
20 Jakhar, K & Makrandi J K, *Indian J Chem*, 52B (2013) 113.

21 Jităreanu A, Zbancioc A-M, Tuchiluş C, Balan M, Stănescu U & Tătărîngă G, *Rev Med Chir Soc Med Nat,* 119 (2015) 1180.
22 Berthelot J, Benammar Y & Desmazières B, *Canadian J Chem*, 73 (1995) 1526.
23 Sangwan N K, *J Chem Res (S),* (1987) 22.
24 Sangwan N K & Rastogi S N, *Indian J Chem,* 18 B (1979) 65.
25 Elguero J & Fruchier A, *J Chem Res (S)*, (1990) 200.
26 Hassner A, Michelson M J, *J Org Chem*, 27 (1962) 3974.
27 Brey W S (Jr) & Valencia C M, *Canadian J Chem*, 46 (1968) 810.
28 Tuite J, *Plant pathological methods: Fungi and bacteria* (Burgess Publishing Company, Minneapolis), 1969, p. l.
29 Singh N, Sangwan N K & Dhindsa K S, *Pest Manag Sci*, 56 (2000) 284.