Indian Journal of Chemistry
Vol. 63, February 2024, pp. 137-144
DOI: 10.56042/ijc.v63i2.4215

Synthesis and evaluation of some novel 2-[4-(1-acyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetic acid hydrazide and amide derivatives as potential pesticides

Heetika Malik, Puspinder Kaur, Anjula Dahiya & Naresh K Sangwan*[#]

Department of Chemistry, CCS Haryana Agricultural University, Hisar 125 004, India

E-mail: nksangwan@gmail.com

Received 25 July 2023; accepted (revised) 19 January 2024

3-Aryl-1-(4-hydroxyphenyl)prop-2-en-1-ones **9**–**15**, prepared by base catalyzed condensation of 4-hydroxyacetophenone (**l**) with araldehydes **2**–**8**, are refluxed with hydrazine hydrate in alkanoic acids to give 1-acyl-5-aryl-4,5-dihydro-3-(4-hydroxyphenyl)-1*H*-pyrazoles **16**–**32**. Alkylation of **16**–**32** with ethyl chloroacetate gives the corresponding substituted phenoxyacetates **33**–**49**. The esters **33**–**49** are subjected to nucleophilic displacement reactions with hydrazine hydrate, isopropylamine, morpholine and piperidine to yield the title compounds, 2-[4-(1-acyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetic acid hydrazide **50**–**66** and amide derivatives **67**–**104**. The compounds are identified with the help of their IR and ^{1}H NMR spectra and elemental analysis. All the compounds are tested for their activity against five phytopathogenic fungi, (*Sclerotinia sclerotiorum*, *Rhizoctonia bataticola*, *Rhizoctonia solani*, *Alternaria brassicae* and *Fusarium solani*), two saprophytic fungi (*Aspergillus niger* and *Penicillium digitatum*) and one phytopathogenic bacterium (*Xanthomonas campestris* pv. *Citrii*). Many compounds inhibit the growth of *S. sclerotiorum* at a concentration of 200 mg litre^{-1}. The compounds **53**, **54** and **78** show non-specific activity against several fungi tested.

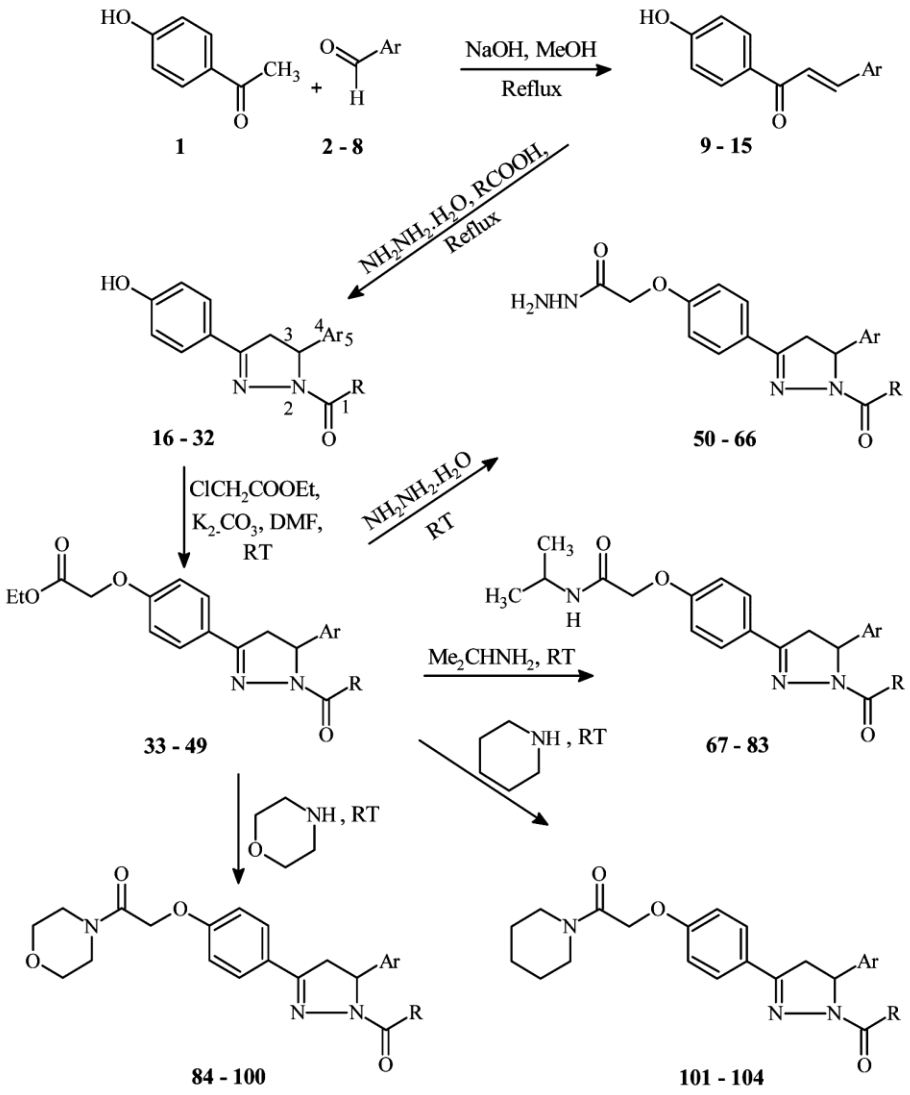
Keywords: 4,5-Dihydropyrazoles, Phenoxyacetic acid hydrazides, Phenoxyacetamides, Antifungal activity, Antibacterial activity

Pesticide resistance, as a result of their continuous use, is one of the foremost problems in crop protection both at preharvest and postharvest stages. This necessitates continuous synthesis of new compounds, which are likely to be used as pesticides, and their primary *in vitro* screening to identify active compounds for further detailed studies. Derivatives of 1*H*-pyrazole[1] and 4,5-dihydro-1*H*-pyrazole[2-9] have gained reputation for their various medicinal and pesticidal activities. In recent years, several such compounds with anticancer[10], cytotoxic[11], antiinflammatory[11-12], antideprassant[13], neurodegenrative[14], enzyme inhibitors[15-17], antimicrobial[18-28], insecticidal[29] and herbicidal[30] activities have been reported. Previously, we have synthesized several phenoxyacetamides[27], [4-(4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetic acid hydrazide derivatives[27] and 1,3-bis[2 or 4-substituted cinnamoyl or 4,5-dihydro-1H-pyrazol-3-ylphenoxy]-2-propanols and related compounds[28] with interesting profile of antifungal activity. In continuation of these studies and to improve upon the activity of such compounds, herein, we report the synthesis of title compounds, 2-[4-(1-acyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetic acid hydrazide and amide derivatives and their *in vitro* growth-inhibitory activity against five phytopathogenic fungi, two saprophytic fungi and one phytopathogenic bacterium of economic importance.

Experimental Section

3-Aryl-1-(4-hydroxyphenyl)prop-2-en-1-ones (**9**–**15,** Scheme 1), required as starting materials were prepared by condensation of 4-hydroxyacetophenone (**1**) with substituted araldehydes (**2**–**8**) in refluxing 4% methanolic sodium hydroxide using literature procedure[26]. The melting points were determined in open capillaries on a Ganson electric melting point apparatus and are uncorrected. Homogeneity of the compounds was routinely checked on silica gel G TLC plates using ethyl acetate : hexane (3 : 7) as eluent. The IR spectra were run on a "Biorad FT-IR" spectrophotometer in KBr pallets and frequencies are expressed in cm^{-1}. The ^{1}H NMR spectra were recorded on "Bruker AM 300" (300 MHz) instrument

Professor of Chemistry now retired from CCS HAU, Hisar



Scheme 1 — Synthesis of acetic acid hydrazide and amide derivatives

in deuterochloroform ($CDCl_3$) or otherwise stated using tetramethylsilane as 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 values.

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

1-Acetyl-5-(4-chlorophenyl)-4,5-dihydro-3-(4-hydroxyphenyl)-1*H*-pyrazole, 22

A mixture of **12** (2.59 g; 10 mmol), hydrazine hydrate (4.0 ml; excess) and glacial acetic acid (10 ml) was refluxed for 10 h. The reaction mixture was cooled and poured into ice-water with stirring. The separated solid was filtered, washed thoroughly with water, dried and recrystallized from methanol to give 2.74 g of **22,** yield 87%, mp 210°C. IR: 3142 (OH), 1640 (C=O); ^{1}H NMR: 2.32 (s, 3H, C*H*$_3$), 3.05 (dd, 1H, *trans* C$_4$-*H*, *J* = 5 and 18 Hz), 3.72 (dd, 1H, *cis* C$_4$-*H*, *J* = 12 and 18 Hz), 5.50 (dd, 1H, C$_5$-*H*, *J* = 5

Table 1 — Structure and characterization data of title and intermediate compounds

Compd [a]	Ar [b]	R	m.p. (°C)	Yield (%)	Mol. Formula [c]
16	C_6H_5-	H	200	67	$C_{16}H_{14}N_2O_2$
17	4-MeC_6H_4-	H	163	87	$C_{17}H_{16}N_2O_2$
18	4-$MeOC_6H_4$-	H	210	91	$C_{17}H_{16}N_2O_3$
19	C_6H_5-	Me	210	86	$C_{17}H_{16}N_2O_2$
20	4-MeC_6H_4-	Me	254	84	$C_{18}H_{18}N_2O_2$
21	4-$MeOC_6H_4$-	Me	220	80	$C_{18}H_{18}N_2O_3$
22	4-ClC_6H_4-	Me	210	87	$C_{17}H_{15}ClN_2O_2$
23	3-$NO_2C_6H_4$-	Me	218	81	$C_{17}H_{15}N_3O_4$
24	3,4,5-$(MeO)_3C_6H_2$-	Me	205	87	$C_{20}H_{22}N_2O_5$
25	2-Furyl	Me	210	84	$C_{15}H_{14}N_2O_3$
26	C_6H_5-	Et	222	87	$C_{18}H_{18}N_2O_2$
27	4-MeC_6H_4-	Et	190	80	$C_{19}H_{20}N_2O_2$
28	4-$MeOC_6H_4$-	Et	202	83	$C_{19}H_{20}N_2O_3$
29	4-ClC_6H_4-	Et	245	88	$C_{18}H_{17}ClN_2O_2$
30	3-$NO_2C_6H_4$-	Et	210	85	$C_{18}H_{17}N_3O_4$
31	3,4,5-$(MeO)_3C_6H_2$-	Et	232	88	$C_{21}H_{24}N_2O_5$
32	2-Furyl	Et	150	84	$C_{16}H_{16}N_2O_3$
33	C_6H_5-	H	80	89	$C_{20}H_{20}N_2O_4$
34	4-MeC_6H_4-	H	112	88	$C_{21}H_{22}N_2O_4$
35	4-$MeOC_6H_4$-	H	68	85	$C_{21}H_{22}N_2O_5$
36	C_6H_5-	Me	101	85	$C_{21}H_{22}N_2O_4$
37	4-MeC_6H_4-	Me	110	86	$C_{22}H_{24}N_2O_4$
38	4-$MeOC_6H_4$-	Me	130	82	$C_{22}H_{24}N_2O_5$
39	4-ClC_6H_4-	Me	95	85	$C_{21}H_{21}ClN_2O_4$
40	3-$NO_2C_6H_4$-	Me	118	88	$C_{21}H_{21}N_3O_6$
41	3,4,5-$(MeO)_3C_6H_2$-	Me	98	87	$C_{24}H_{28}N_2O_7$
42	2-Furyl	Me	83	87	$C_{19}H_{20}N_2O_5$
43	C_6H_5-	Et	85	87	$C_{22}H_{24}N_2O_4$
44	4-MeC_6H_4-	Et	105	89	$C_{23}H_{26}N_2O_4$
45	4-$MeOC_6H_4$-	Et	96	85	$C_{23}H_{26}N_2O_5$
46	4-ClC_6H_4-	Et	75	85	$C_{22}H_{23}ClN_2O_4$
47	3-$NO_2C_6H_4$-	Et	112	84	$C_{22}H_{23}N_3O_6$
48	3,4,5-$(MeO)_3C_6H_2$-	Et	122	89	$C_{25}H_{30}N_2O_7$
49	2-Furyl	Et	82	87	$C_{20}H_{22}N_2O_5$
50	C_6H_5-	H	143	81	$C_{18}H_{18}N_4O_3$
51	4-MeC_6H_4-	H	160	83	$C_{19}H_{20}N_4O_3$
52	4-$MeOC_6H_4$-	H	135	79	$C_{19}H_{20}N_4O_4$
53	C_6H_5-	Me	125	88	$C_{19}H_{20}N_4O_3$
54	4-MeC_6H_4-	Me	130	84	$C_{20}H_{22}N_4O_3$
55	4-$MeOC_6H_4$-	Me	115	80	$C_{20}H_{22}N_4O_4$
56	4-ClC_6H_4-	Me	95	87	$C_{19}H_{19}ClN_4O_3$
57	3-$NO_2C_6H_4$-	Me	168	83	$C_{19}H_{19}N_5O_5$
58	3,4,5-$(MeO)_3C_6H_2$-	Me	128	84	$C_{22}H_{26}N_4O_6$
59	2-Furyl	Me	145	82	$C_{17}H_{18}N_4O_4$
60	C_6H_5-	Et	Gum	76	$C_{20}H_{22}N_4O_3$
61	4-MeC_6H_4-	Et	182	89	$C_{21}H_{24}N_4O_3$
62	4-$MeOC_6H_4$-	Et	88	81	$C_{21}H_{24}N_4O_4$
63	4-ClC_6H_4-	Et	154	78	$C_{20}H_{21}ClN_4O_3$

(*Contd.*)

Table 1 — Structure and characterization data of title and intermediate compounds (*Contd*.)

Compd [a]	Ar [b]	R	m.p. (°C)	Yield (%)	Mol. Formula [c]
64	3-$NO_2C_6H_4$-	Et	145	81	$C_{20}H_{21}N_5O_5$
65	3,4,5-$(MeO)_3C_6H_2$-	Et	130	87	$C_{23}H_{28}N_4O_6$
66	2-Furyl	Et	75	86	$C_{18}H_{20}N_4O_4$
67	C_6H_5-	H	130	50	$C_{21}H_{23}N_3O_3$
68	4-MeC_6H_4-	H	152	86	$C_{22}H_{25}N_3O_3$
69	4-$MeOC_6H_4$-	H	160	50	$C_{22}H_{25}N_3O_4$
70	C_6H_5-	Me	97	78	$C_{22}H_{25}N_3O_3$
71	4-MeC_6H_4-	Me	Gum	74	$C_{23}H_{27}N_3O_3$
72	4-$MeOC_6H_4$-	Me	162	82	$C_{23}H_{27}N_3O_4$
73	4-ClC_6H_4-	Me	145	86	$C_{22}H_{24}ClN_3O_3$
74	3-$NO_2C_6H_4$-	Me	165	84	$C_{22}H_{24}N_4O_5$
75	3,4,5-$(MeO)_3C_6H_2$-	Me	Gum	76	$C_{25}H_{31}N_3O_6$
76	2-Furyl	Me	Gum	76	$C_{20}H_{23}N_3O_4$
77	C_6H_5-	Et	Gum	78	$C_{23}H_{27}N_3O_3$
78	4-MeC_6H_4-	Et	155	87	$C_{24}H_{29}N_3O_3$
79	4-$MeOC_6H_4$-	Et	Gum	77	$C_{24}H_{29}N_3O_4$
80	4-ClC_6H_4-	Et	168	83	$C_{23}H_{26}ClN_3O_3$
81	3-$NO_2C_6H_4$-	Et	157	83	$C_{23}H_{26}N_4O_5$
82	3,4,5-$(MeO)_3C_6H_2$-	Et	172	84	$C_{26}H_{33}N_3O_6$
83	2-Furyl	Et	Gum	79	$C_{21}H_{25}N_3O_4$
84	C_6H_5-	H	155	45	$C_{22}H_{23}N_3O_4$
85	4-MeC_6H_4-	H	113	86	$C_{23}H_{25}N_3O_4$
86	4-$MeOC_6H_4$-	H	185	35	$C_{23}H_{25}N_3O_5$
87	C_6H_5-	Me	Gum	79	$C_{23}H_{25}N_3O_4$
88	4-MeC_6H_4-	Me	140	87	$C_{24}H_{27}N_3O_4$
89	4-$MeOC_6H_4$-	Me	135	87	$C_{24}H_{27}N_3O_5$
90	4-ClC_6H_4-	Me	Gum	78	$C_{23}H_{24}ClN_3O_4$
91	3-$NO_2C_6H_4$-	Me	140	81	$C_{23}H_{24}N_4O_6$
92	3,4,5-$(MeO)_3C_6H_2$-	Me	Gum	76	$C_{25}H_{31}N_3O_7$
93	2-Furyl	Me	180	84	$C_{21}H_{23}N_3O_5$
94	C_6H_5-	Et	140	81	$C_{24}H_{27}N_3O_4$
95	4-MeC_6H_4-	Et	117	85	$C_{25}H_{29}N_3O_4$
96	4-$MeOC_6H_4$-	Et	Gum	73	$C_{25}H_{29}N_3O_5$
97	4-ClC_6H_4-	Et	180	84	$C_{24}H_{26}ClN_3O_4$
98	3-$NO_2C_6H_4$-	Et	95	86	$C_{24}H_{26}N_4O_6$
99	3,4,5-$(MeO)_3C_6H_2$-	Et	120	85	$C_{27}H_{33}N_3O_7$
100	2-Furyl	Et	Gum	77	$C_{22}H_{25}N_3O_5$
101	C_6H_5-	H	80	50	$C_{23}H_{25}N_3O_3$
102	4-$MeOC_6H_4$-	H	172	25	$C_{24}H_{27}N_3O_4$
103	C_6H_5-	Me	161	54	$C_{24}H_{27}N_3O_3$
104	4-$MeOC_6H_4$-	Me	112	45	$C_{25}H_{29}N_3O_4$

[a] Compound numbers described here refer to those given in Scheme 1. [b] The substituents Ar in compounds **2**–**8** and also in **9**–**15** are same as in **19**–**25** respectively. [c] The compounds were analyzed for C, H and N within ± 0·4% of the theoretically calculated values.

and 12 Hz), 6.83 (d, 2H, *Arom H o*- to OH, *J* = 9 Hz), 7.18 (d, 2H, *Arom H m*- to Cl, *J* = 8 Hz), 7.29 (d, 2H, *Arom H o*- to Cl, *J* = 8 Hz), 7.57 (d, 2H, *Arom H m*- to OH, *J* = 9 Hz). Anal: Calcd for $C_{17}H_{15}ClN_2O_2$: C, 64.87; H, 4.80; N, 8.90%. Found C, 64.91; H, 4.76; N, 8.97.

Ethyl [4-{1-acetyl-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl}phenoxy]acetate, 39

A mixture of **22** (3.15 g, 10 mmol), ethyl chloroacetate (1.23 g, 10 mmol), anhydrous potassium carbonate (1.38 g, 10 mmol) and dry dimethylformamide (20 ml) was stirred for 24 hours.

The reaction mixture was poured on to ice-water with stirring. The separated gummy product was extracted with ethyl acetate. The extract was washed thoroughly with water and dried over anhydrous sodium sulfate. The solvent was removed by distillation and the residual product was purified by column chromatography over silica gel using ethyl acetate : hexane (20 : 80) as eluant to give 3.40 g of **39**, yield 85%, mp 95°C. IR: 1749 (C=O of ester), 1659 (C=O); ^{1}H NMR: 1.30 (t, 3H, CH_2CH_3, J = 7 Hz), 2.39 (s, 3H, $COCH_3$), 3.08 (dd, 1H, *trans* C_4-*H*, J = 5 and 18 Hz), 3.71 (dd, 1H, *cis* C_4-*H*, J = 12 and 18 Hz), 4.28 (q, 2H, CH_2CH_3, J = 7 Hz), 4.66 (s, 2H, OCH_2), 5.53 (dd, 1H, C_5-*H*, J = 5 and 12 Hz), 6.94 (d, 2H, *Arom H o-* to OCH_2, J = 9 Hz), 7.16 (d, 2H, *Arom H m-* to Cl, J = 8 Hz), 7.28 (d, 2H, *Arom H o-* to Cl, J = 8 Hz), 7.68 (d, 2H, *Arom H m-* to OCH_2, J = 9 Hz). Anal. Calcd. for $C_{21}H_{21}ClN_2O_4$: C, 62.92; H, 5.28; N, 6.99%. Found: C, 62.94; H, 5.37; N, 7.02.

2-[4-{1-Acetyl-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl}phenoxy]acetic acid hydrazide, 56

A solution of **39** (0.4 g, 1 mmol) and hydrazine hydrate (1 ml, excess) in absolute ethanol (5 ml) was refluxed for 1 hour. The reaction mixture was cooled and poured onto ice-water with stirring. The separated solid was filtered, washed thoroughly with water, dried and recrystallized from methanol to give 0.33 g of **56**, yield 87%, mp 95°C. IR: 3255 (NH, NH_2), 1664 (C=O); ^{1}H NMR: 2.40 (s, 3H, $COCH_3$), 3.08 (dd, 1H, *trans* C_4-*H*, J = 5 and 18 Hz), 3.72 (dd, 1H, *cis* C_4-*H*, J = 12 and 18 Hz), 4.62 (s, 2H, OCH_2), 5.55 (dd, 1H, C_5-H, J = 5 and 12 Hz), 6.95 (d, 2H, Arom *H o-* to OCH_2, J = 9 Hz), 7.16 (d, 2H, Arom *H m-* to Cl, J = 8 Hz), 7.29 (d, 2H, Arom *H o-* to Cl, J = 8 Hz), 7.71 (d, 2H, Arom *H m-* to OCH_2, J = 9 Hz). Anal. Calcd. for $C_{19}H_{19}ClN_4O_3$: C, 58.99; H, 4.95; N, 14.48%. Found: C, 58.96; H, 4.97; N, 14.54.

2-[4-{1-Acetyl-5-(4-chlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl}phenoxy]-N-isopropylacetamide, 73

A solution of **39** (0.4 g, 1 mmol) in isopropylamine (2 ml; excess) was allowed to stand at room temperature for 10 days. The solution was diluted with ice-cold water. The separated solid was filtered, washed with water, dried, and crystallized from methanol to give 0.36 g of **73**, yield 86%, mp 145°C. IR: 3294 (NH), 1657 (broad, C=O of amide and C=O of $COCH_3$); ^{1}H NMR: 1.21 (d, 6H, 2 × CH_3, J = 7 Hz), 2.40 (s, 3H, CH_3), 3.09 (dd, 1H, *trans* C_4-*H*, J = 5 and 18 Hz), 3.73 (dd, 1H, *cis* C_4-*H*, J = 12 and 18 Hz), 4.20 (m, 1H, C*H*), 4.49 (s, 2H, OCH_2), 5.55 (dd, 1H, C_5-H, J = 5 and 12 Hz), 6.97(d, 2H, Arom *H o-* to OCH_2, J = 9 Hz), 7.16 (d, 2H, Arom *H m-* to Cl, J = 9 Hz), 7.25 (d, 2H, Arom *H o-* to Cl, J = 9 Hz), 7.71 (d, 2H, Arom *H m-* to OCH_2, J = 9 Hz). Anal. Calcd. for $C_{22}H_{24}ClN_3O_3$: C, 63.84; H, 5.84; N, 10.15%. Found C, 63.88; H, 5.91; N, 10.19.

4-[[4-{1-Acetyl-4,5-dihydro-5-(4-chlorophenyl)-1*H*-pyrazol-3-yl}phenoxy]acetyl]morpholine, 90

A mixture of **39** (0.4 g, 1 mmol) and morpholine (2 ml; excess) was allowed to stand at room temperature for 10 days with occasional shaking. The reaction mixture was poured onto ice-cold water with stirring and the separated gummy product was extracted with ethyl acetate. The extract was washed with water several times and dried over anhydrous sodium sulfate. The solvent was stripped off from the extract by distillation and the residue was purified by column chromatography over silica gel using ethyl acetate : hexane (20 : 80) as eluant to give 0.34 g of **90**, yield 78% as a gummy solid. IR: 1650 (broad, C=O); ^{1}H NMR: 2.39 (s, 3H, $COCH_3$), 3.09 (dd, 1H, *trans* C_4-*H*, J = 5 and 18 Hz), 3.65 (m, 1H, *cis* C_4-*H* and morpholinyl-*H*), 4.74 (s, 2H, OCH_2), 5.54 (dd, 1H, C_5-*H*, J = 5 and 12 Hz), 6.96 (d, 2H, *Arom H o-* to OCH_2, J = 9 Hz), 7.18 (d, 2H, *Arom H m-* to Cl, J = 9 Hz), 7.24 (d, 2H, *Arom H o-* to Cl, J = 9 Hz), 7.73 (d, 2H, *Arom H m-* to OCH_2, J = 9 Hz). Anal. Calcd. for $C_{23}H_{24}ClN_3O_4$: C, 62.51; H, 5.48; N, 9.51%. Found: C, 62.82; H, 5.68; N, 9.19.

1-[[4-{1-Acetyl-4,5-dihydro-5-(4-methoxyphenyl)-1*H*-pyrazol-3-yl}phenoxy]acetyl]piperidine, 104

A mixture of **38** (0.4 g, 1 mmol) and piperidine (2 ml; excess) was allowed to stand at room temperature for 10 days with occasional shaking. The reaction mixture was poured onto ice-cold water with stirring and the separated gummy product was extracted with ethyl acetate. The extract was washed with water several times and dried over anhydrous sodium sulfate. The solvent was stripped off from the extract by distillation and the residue was purified by column chromatography over silica gel using ethyl acetate : hexane (20 : 80) as eluant to give 0.2 g of **104**, yield 45%, mp 112°C. IR: 1640 (broad, C=O); ^{1}H NMR (CCl_4): 1.57 (m, 6H, $CH_2CH_2CH_2$), 2.33 (s, 3H. $COCH_3$), 3.47 (m, 4H, CH_2NCH_2), 3.73 (s, 3H, OCH_3), 4.60 (s, 2H, OCH_2), 6.65 (d, 2H, *Arom H, o-*

to OCH_2, J = 9 Hz), 6.87 (d, 2H, *Arom H*, *o*- to OCH_3, J = 9 Hz), 7.00 (d, 2H, *Arom H*, *m*- to OCH_3, J = 9 Hz), 7.57 (d, 2H, *Arom H*, *m*- to OCH_2, J = 9 Hz). Anal. Calcd. for $C_{25}H_{29}N_3O_4$: C, 68.95; H, 6.71; N, 9.64%. Found: C, 69.21; H, 6.48; N, 9.76.

Bioassay

The stock solution (double strength) of the test compound (10 mg) was prepared, in DMSO (2.5 ml) and diluted with distilled and sterilized water to a final volume of 25 ml to provide a stock solution of 400 mg litre^{-1} concentration. The commercial fungicide carbendazim was used as a standard for comparing the activity of the test compounds. It was used as a commercial 500 g kg^{-1} WP (Bavistin, BASF).

All the synthesized compounds (**16**–**104**) were screened for their activity against five phytopathogenic fungi, [*Sclerotinia sclerotiorum* (Lib.) de Bary from rapeseed - mustard, *Rhizoctonia bataticola* (Taub.) Butler from mungbean, *Rhizoctonia solani* Kuhn. from cauliflower, *Alternaria brassicae* (Berk.) Sacc. from rapeseed-mustard and *Fusarium solani* (Mart.) Sacc. from tomato], two saprophytic fungi (*Aspergillus niger* Van Tieghem, *Penicillium digitatum* Sacc.) and one phytopathogenic bacterium [*Xanthomonas campestris* pv. *citrii* (Hasse) Dowson from citrus].

Antifungal Activity

The compounds **16**–**104** were tested against the microorganisms by the reported poison food technique[31]. Double strength potato-dextrose-agar (PDA) medium (20 ml) was sterilized in 100 ml conical flasks. The stock solution (double strength) of the test compound (20 ml) was then mixed thoroughly into the sterilized medium aseptically and poured into Petri plates (20 ml each) to give a test solution concentration of 200 mg litre^{-1}. For testing antifungal activity, five mm discs of the fungal growth from seven days old culture on PDA medium maintained at 28±1°C were cut and transferred aseptically in the Petri plates containing pre-amended/impregnated medium. The Petri plates were then transferred into the BOD incubator maintained at 28±1°C. The growth of the fungal colony was observed daily for five days. The compound, which prevented the growth of microorganism under evaluation completely, was considered active. The compounds, which were found active at 200 mg litre^{-1}, were similarly tested at lower concentration of 100, 50, 25, 12.5 and 6.25 mg litre^{-1}. The lowest concentration of the compound at which no growth of the microorganism observed was taken to represent the minimum inhibitory concentration (MIC).

Antibacterial activity

The compounds were tested against the bacterium *X. campestris* pv. *citrii* by using the similar procedure as described for antifungal activity except that a small loop of bacterium from five-day old culture instead of disc was used.

Results and Discussion

Cyclization of 3-aryl-1-(4-hydroxyphenyl)prop-2-en-1-ones (**9**–**15**) by refluxing these with hydrazine hydrate in suitable alkanoic acid (formic, acetic or propionic acids) gave the corresponding 1-acyl-5-aryl-4,5-dihydro-3-(4-hydroxyphenyl)-1*H*-pyrazoles (**16**–**32**) in good yields (Table 1). The compounds displayed characteristic ^{1}H NMR spectra. The geminal protons at C-4, that are adjacent to the chiral centre at C-5, showed magnetic non-equivalence and, therefore, appeared at different chemical shifts. 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[26-28, 32,33] and elsewhere[34].

Alkylation of (**16**–**32)** with ethyl chloroacetate in dimethylformamide in presence of anhydrous potassium carbonate at ambient temperature gave ethyl [4-(1-acyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetates **(33**–**49),** respectively, in good yields. The compounds showed characteristic absorption bands around 1760 cm^{-1} for the carbonyl of ester group. The ^{1}H NMR spectra displayed additional triplet and quartet of methyl and methylene protons of –COOCH_2CH_3 with expected coupling constants (7 Hz) and a singlet for methylene protons of OCH_2COOEt at their characteristic chemical shifts.

The ethyl esters **33**–**49,** when subjected to nucleophilic displacement reactions with excess of hydrazine hydrate in refluxing absolute alcohol, gave the title compound, 2-[4-(1-acyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetic acid hydrazides (**50**–**66**) in good yields. The other series of title compounds, 2-[4-(1-acyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]-N-isopropylacetamides (**67**–**83**) and 4-[{4-(1-acyl-5-aryl-4,5-dihydro-1*H*-pyrazol-

3-yl)phenoxy}acetyl]morpholines (**84–100**) were prepared by the reaction of ethyl esters **33–49** with isopropylamine and morpholine respectively at room temperature. In a similar manner, some analogous piperidine derivatives, 1-[{4-(1-Acyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy}acetyl]piperidines (**101–104**), were also prepared by the reaction of the ethyl esters **33**, **35, 36** and **38**, respectively with piperidine. The compounds were identified by their IR and ^{1}H NMR spectra and elemental analyses.

Pesticidal activity

The growth-inhibitory activity *in vitro* of the compounds against four pathogenic and two saprophytic fungi are shown in Table 2. All the compounds were ineffective in preventing the growth of the fungus *F. solani* and the bacterium *X. campestris pv. citrii* up to a concentration of 200 mg litre^{-1}. The compounds not included in the Table 2 also did not prevent the growth of any of the fungi and bacterium tested up to a concentration of 200 mg litre^{-1}. The standard, carbendazim, inhibited the growth of all tested microorganisms upto the lowest evaluated concentration of 6.25 mg litre^{-1}.

A perusal of the data indicates that the compounds were mainly active against *S. sclerotiorum* at a concentration of 200 mg litre^{-1} though a few compounds were active also at lower concentrations of 100 mg litre^{-1} (**53, 64, 78 and 82**) and 50 mg litre^{-1} (**54, 59 and 98**). The growth of *R. bataticola* was inhibited by **53**, **54**, **78** and **82** at 200 mg litre^{-1} and by **73** at 100 mg litre^{-1} concentrations. Only four compounds **53**, **54**, **64** and **78** registered their activity against *R. solani* at 200 mg litre^{-1} concentration. *A. brassicae* was found sensitive to **36**, **53**, **61**, **64** and **78** at 200 mg litre^{-1} and to **54** and **73** at 100 mg litre^{-1} concentrations. The saprophytic fungi were found insensitive to many of the compounds evaluated as only two compounds **54** and **59** were found active against *A. niger* at 50 and 100 mg litre^{-1}

Table 2 — Growth-inhibitory activity *in vitro* of title and intermediate compounds[a]

Compd[b]	Minimum inhibitory concentration[b] (mg litre^{-1}) against[c]					
	S. sclerotiorum	*R. bataticola*	*R. solani*	*A. brassicae*	*A. niger*	*P. digitatum*
36	200	–	–	200	–	–
38	200	–	–	–	–	–
43	200	–	–	–	–	–
51	200	–	–	–	–	–
53	100	200	200	200	–	–
54	50	200	200	100	50	–
56	200	–	–	–	–	–
57	200	–	–	–	–	–
58	200	–	–	–	–	–
59	50	–	–	–	100	–
61	200	–	–	200	–	–
64	100	–	200	200	–	–
65	200	–	–	–	–	–
66	200	–	–	–	–	–
70	200	–	–	–	–	–
73	–	100	–	100	–	–
78	100	200	200	200	–	200
82	100	200	–	–	–	–
88	200	–	–	–	–	–
93	200	–	–	–	–	–
94	200	–	–	–	–	–
96	200	–	–	–	–	–
98	50	–	–	–	–	–

[a] Compounds not included in this table were found ineffective in preventing the growth of any of the tested fungi or bacterium up to a concentration of 200 mg litre^{-1}.

[b] Compound Nos. given in this column refer to those described in Scheme 1 and Table 1.

[c] Dash "–" indicates that the compound did not prevent the growth of the fungus upto a concentration of 200 mg litre^{-1}

concentrations respectively and only one compound **78** against *P. digitatum* at 200 mg litre^{-1} concentration.

In general, majority of the synthesized substituted phenoxyacetic acid hydrazides (**50–66**) were found active against the tested phytopathogenic fungi, whereas only a few of substituted phenoxyacetic acid esters (**33–49**) and substituted phenoxyacetamides (**67–104**) were found active. However, none of the compounds showed comparable activity to that of carbendazim against any of the tested organisms. The non-specific activity shown by some of the compounds, **53**, **54 and 78,** against several fungi tested and specific activity shown by many of the compounds against fungus *S. sclerotiorum* may provide suitable leads to develop both non-specific and specific fungitoxic compounds.

Conclusion

Several 2-[4-(1-acyl-5-aryl-4,5-dihydro-1*H*-pyrazol-3-yl)phenoxy]acetic acid hydrazides and amides are synthesized and characterized by their spectral and elemental analysis. All the compounds are evaluated for their antimicrobial activity against five phytopathogenic fungi, two saprophytic fungi and one phytopathogenic bacterium. Many of the compounds show specific antifungal activity against *S. sclerotiorum.* Some of the compounds also showed non-specific antifungal activity against several fungi tested. Although none of the compounds surpass the activity of carbendazim, but this is likely to be improved 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 Yet L, *Comprehensive Heterocyclic Chemistry IV*, 4 (2022) 1.
2 Sharma S, Kaur S, Bansal T & Gaba J, *Chem Sci Trans*, 3 (2014) 861.
3 Mathew A T, Chandran M, Geetha Elias G, Swathy P S & Krishnakumar K, Intern *J Res Rev, 8* (2021) 174.
4 Swathi V, Sudev S, Dhanya K, Jose A & Sreelakshmi, *J Med Sci Clinical Res*, 7 (2019) 612.
5 Varghese B, Al-Busafi S N, Suliman F E O & Al-Kindy S M Z, *RSC Adv*, 7 (2017) 46999.
6 Naim M J, Alam O, Nawaz F, Alam M J & Alam P, *J Pharm Bioall Sci*, 8 (2016) 2.
7 Khan M F, Alam M M, Verma G, Akhtar W, Akhter M, Shaquiquzzaman M, *Eur J Med Chem*, 120 (2016) 170.
8 Karrouchi K, Radi S, Ramli Y, Taoufik J, Mabkhot Y N, Al-aizari F A & Ansar M, *Molecules*, 23 (2018) 134.
9 Muralidharan V, Asha Deepti C & Raja S, Int *J Pharm Pharma Sci*, 10 (2018) 9.
10 Kashif Haider K, Shafeque M, Yahya S & Yar M S, *Eur J Med Chem Reports*, 5 (2022) 100042.
11 Hamada N M M, & Abdo N Y M, *Molecules*, 20 (2015) 10468.
12 Zhang Z, Cao P, Fang M, Zou T, Han J, Duan Y, Xu H, Yang X & Li Q -S, *Eur J Med Chem*, 225 (2021) 113743.
13 Palaska E, Aytemir M, Uzbay T & Erol D, *Eur J Med Chem*, 36 (2001) 539.
14 Ahsan M J, Ali A, Ali A, Thiriveedhi A, Bakht M A, Yusuf M, Salahuddin, Afzal O & Altamimi A S A, *ACS Omega*, 7 (2022) 38207.
15 Ozgun D O, Gul H I, Yamali C, Sakagami H, Gulcin I, Sukuroglu M & Supuran C T, *Bioorg Chem*, 84 (2019) 511,
16 Manna F, Chimenti F, Bolasco A, Secci D, Bizzarri B, Befani O, Turini P, Mondovı B, Alcaroc S & Tafi A, *Bioorg Med Chem Lett*, 12 (2002) 3629.
17 Fioravanti R, Bolasco A, Manna F, Rossi F, Orallo F, Ortuso F, Alcaro S & Cirilli R, *Eur J Med Chem*, 45 (2010) 6135.
18 Jain S K, Singhal R & Jain N K, *Research J Pharm Technol*, 14 (2021) 6223.
19 Singh N, Sangwan N K & Dhindsa K S, *Synth React Inorg Metal-Org Chem*, 29 (1999) 673.
20 Khan S S & Hasan A, *Heterocyclic Comm*, 13 (2007) 131.
21 Singh N, Sangwan N K & Dhindsa K S, *J Indian Chem Soc*, 78 (2001) 119.
22 Singh N, Sangwan N K & Dhindsa K S, *Pest Manag Sci*, 56 (2000) 284.
23 *Asad M, Arshad M N, Oves M, Khalid M, Khan S A, Asiri A M, Rehan M & Dzudzevic-Cancar H, Bioorg Chem*, 99 (2020) 103842.
24 Wong K T, Osman H, Parumasivam T, Supratman U, Omar M T C & Azmi M N, *Molecules*, 26 (2021) 2081.
25 Revanasiddappa B C, Jisha M S, Kumar M V & Kumar H, *Dhaka Univ J Pharm Sci*, 17 (2018) 221.
26 Saini C & Sangwan N K, *Indian J Chem*, 61 (2022) 1257.
27 Malik H, Dahiya A, Kumar R, Sangwan M S, Mehta N & Sangwan N K, *Indian J Chem*, 40 B (2001) 682.
28 Sangwan N K, Verma B S & Dhindsa K S, *Indian J Chem*, 31 (1992) 590.
29 Wu J, Song B -A, Hu D -Y, Yue M & Yang S, *Pest Manag Sci*, 68 (2012) 801.
30 Cai Z, Zhang W, Yan Z & Du X, *Molecules*, 27 (2022) 6274.
31 Dhingra O D & Sinclair J B, *Basic Plant Pathology Methods, Second Ed.*, (CRC Press Inc, Florida) 2019, pp 272.
32 Sangwan N K, *J Chem Res (S),* (1987) 22. https://pubs.rsc.org/en/content/articlepdf/1987/dt/dt98700bx007
33 Sangwan N K & Rastogi S N, *Indian J Chem*, 18 B (1979) 65.
34 Elguero J & Fruchier A, *J Chem Res (S),* (1990) 200; https://pubs.rsc.org/en/content/articlepdf/1990/p1/p199000bx031