Synthesis and biological activity of hydrazone derivatives containing pyrazole

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Twelve novel hydrazone derivatives containing pyrazole rings have been prepared by condensing substituted-benzaldehyde with 2-(3,5-dimethyl-*1H*-pyrazol-1-yl)acetohydrazide under microwave irradiation. Their structures were characterised by ^{1}H NMR, IR, MS and elemental analysis. The preliminary biological activity tests showed that some of the compounds showed moderate fungicidal activity.

Keywords: hydrazone, pyrazole, microwave irradiation, fungicidal activity

Pyrazoles are a class of heterocyclic compounds that have many derivatives with biological activities, such as antiviral,[1] antitumor,[2] anti-inflammatory,[3] analgesic,[4] anti-bacterial,[5] kidney aldose reductase,[6] herbicidal,[7] insecticidal.[8] Recently, some pyrazole derivatives were reported to have fungicidal activity.[9] The pyrazole moiety is a core structure in a number of biologically active compounds. Meanwhile, Schiff bases exhibit good biological activity, such as pesticidal[10] and medicinal[11] activity.

The relatively low cost of modern domestic microwave ovens makes them readily available to academic and industrial chemists, and the use of such unconventional reaction conditions reveals several features such as a short reaction time compared to conventional heating, reduction of the usual thermal degradation, and better selectivity.[13] An attractive synthetic methodology is the possibility of performing reactions in solvent-free conditions or on solid inorganic supports.

In continuation of our interest in organic reactions under microwave irradiation and their biological activities, we now report the synthesis of hydrazones contain pyrazoles under microwave irradiation.

Experimental

Melting points were determined using a Yanaco MP-241 apparatus and were uncorrected. ^{1}H NMR spectra were measured on a Bruker AC-P500 instrument (300 MHz) using tetramethylsilane as an internal standard and deuterochloroform as solvent. Mass spectra were recorded on a Thermo Finnigan LCQ Advantage LC/mass detector instrument. Elemental analyses were performed on a Yanaco MT-3CHN elemental analyser. LWMC-250 domestic microwave oven was used to do microwave reaction.

The title compounds were synthesised according to the route shown in Fig. 1, and the yields were not optimised.

General procedure for **8a-l**

A mixture of acetylacetone (7.0 g, 0.12 mol) and hydrazine hydrate (7.0 g, 85%) was refluxed for 3 h in alcohol and evaporated to alcohol. To this, acetone (20 ml), ethyl chloroacetate (6.13 g, 7.01 ml) and solid K_2CO_3 (6.91 g) were added and the resulting mixture was refluxed for 18 h. Then added hydrazine hydrate (1.34 g, 26.8 mmol) and alcohol (8 ml) was stirred for 4 h at the room temperature. Compound **3** was obtained in 86.4%, the m.p. is also according with reference.[7] Then, the substituted aromatic aldehyde were added to a solution of **3** in ethanol at 300W for 5 min under microwave irradiation, the correspondence productions were obtained. The product was filtered, washed with ethanol, dried, and recrystallised from EtOH to give the title compounds **4a–l**.

N′-(4-chlorobenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl) acetohydrazide (**4a**): White crystal 93.5% yield; m.p. 204–205 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.78(s, CH, 1H), 8.76(s, NH, 1H), 7.27–8.35(m, ArH, 4H), 5.91(s, PyH, 1H), 5.28(s, Py-CH_2, 2H), 2.30(s, Py-CH_3, 3H), 2.27(s, Py-CH_3, 3H). IR(KBr) ν: 3209 (N–H), 1680 (C=O), 1619 (C=N); MS (ESI), *m/z*: 289 (M – 1). Elemental anal. (%), calcd for $C_{14}H_{15}ClN_4O$: C, 57.83; H, 5.20; N, 19.27; found: C, 57.80; H, 5.41; N, 19.51.

N′-(2-bromobenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl) acetohydrazide (**4b**): White crystal 92.1% yield; m.p. 209–210 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.25(s, CH, 1H), 8.43(s, NH, 1H), 7.44–8.15(m, ArH, 4H), 5.69(s, PyH, 1H), 5.21(s, Py-CH_2, 2H), 2.43(s, Py-CH_3, 3H), 2.07(s, Py-CH_3, 3H). IR(KBr) ν: 3234 (N–H), 1685 (C=O), 1615 (C=N); MS (ESI), *m/z*: 334 (M – 1). Elemental anal. (%), calcd for $C_{14}H_{15}BrN_4O$: C, 50.16; H, 4.51; N, 16.71; found: C, 50.49; H, 4.25; N, 17.06.

N′-(4-bromobenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl) acetohydrazide (**4c**): White crystal 92.5% yield; m.p. 186–187 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.32(s, CH, 1H), 8.13(s, NH, 1H), 7.12–7.99(m, ArH, 4H), 5.75(s, PyH, 1H), 5.43(s, Py-CH_2, 2H), 2.61(s, Py-CH_3, 3H), 2.37(s, Py-CH_3, 3H). IR(KBr) ν: 3276 (N–H), 1667 (C=O), 1601 (C=N); MS (ESI), *m/z*: 334 (M – 1). Elemental anal. (%), calcd for $C_{14}H_{15}BrN_4O$: C, 50.16; H, 4.51; N, 16.71; found: C, 50.10; H, 4.77; N, 16.78.

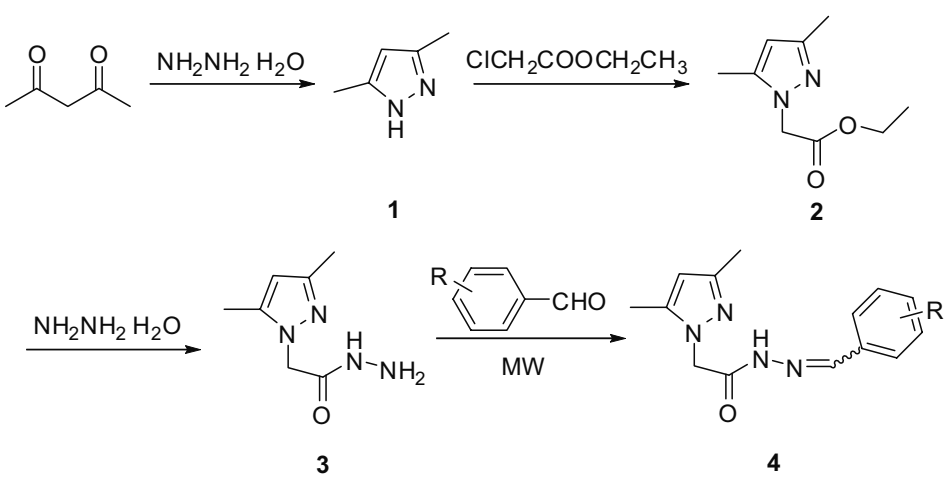

Fig. 1 Synthetic route for compounds **4a–l.**

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Table 1 The fungicidal activity of tested compounds *in vivo* at 500 ppm

No.	*Corynespora cassiicola*	*Cladosporium cucumerinum*	*Erysiphe cichoracearum*	*Sclerotinia sclerotiorum*(Lib.) de Bary	*Colletotrichum orbiculare* (Berk aLMont) Arx.
4a	86.00	13.00	47.40	4.89	81.22
4b	37.00	5.00	54.31	12.79	57.63
4c	43.00	10.00	44.16	33.75	56.18
4d	11.00	25.00	27.17	4.59	73.40
4e	46.00	59.00	75.14	6.08	69.33
4f	45.00	40.00	-5.20	6.08	14.93
4g	7.00	60.00	50.86	31.23	54.50
4h	-0.05	4.00	1.83	16.34	12.99
4i	15.00	30.00	10.00	24.23	45.11
4j	15.00	30.00	10.00	24.23	45.11
4k	62.00	16.00	45.67	41.29	32.82
4l	25.00	6.00	38.22	33.34	50.82

N′-(2-fluorobenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl)acetohydrazide (**4d**): White crystal 97.6% yield; m.p. 177–178 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.82(s, CH, 1H), 8.88(s, NH, 1H), 7.04–8.21(m, ArH, 4H), 5.88(s, PyH, 1H), 5.30(s, Py-CH_2, 2H), 2.22(s, Py-CH_3, 3H), 2.30(s, Py-CH_3, 3H). IR(KBr) ν: 3294 (N–H), 1689 (C=O), 1629 (C=N); MS (ESI), *m/z*: 273 (M – 1). Elemental anal. (%), calcd for $C_{14}H_{15}FN_4O$: C, 61.30; H, 5.51; N, 20.43; found: C, 61.69; H, 5.05; N, 20.62.

N′-(3-methoxybenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl) acetohydrazide (**4e**): White crystal 90.0% yield; m.p. 172–173 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.67(s, CH, 1H), 8.33(s, NH, 1H), 7.41–8.32(m, ArH, 4H), 5.66(s, PyH, 1H), 5.33(s, Py-CH_2, 2H), 3.89(s, O-CH_3, 3H), 2.34(s, Py-CH_3, 3H), 2.27(s, Py-CH_3, 3H). IR(KBr) ν: 3301 (N–H), 1691 (C=O), 1609 (C=N); MS (ESI), *m/z*: 285 (M – 1). Elemental anal. (%), calcd for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57; found: C, 62.88; H, 6.77; N, 19.49.

N′-(4-methoxybenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl) acetohydrazide (**4f**): White crystal 95.3% yield; m.p. 173–174 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.87(s, CH, 1H), 8.44(s, NH, 1H), 7.15–8.21(m, ArH, 4H), 5.70(s, PyH, 1H), 5.41(s, Py-CH_2, 2H), 3.78(s, O-CH_3, 3H), 2.44(s, Py-CH_3, 3H), 2.31(s, Py-CH_3, 3H). IR(KBr) ν: 3210 (N–H), 1678 (C=O), 1620 (C=N); MS (ESI), *m/z*: 285 (M – 1). Elemental anal. (%), calcd for $C_{15}H_{18}N_4O_2$: C, 62.92; H, 6.34; N, 19.57; found: C, 62.77; H, 6.12; N, 19.88.

N′-(4-methybenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl) acetohydrazide (**4g**): White crystal 94.3% yield; m.p. 166–167 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.99(s, CH, 1H), 8.54(s, NH, 1H), 7.45–8.11(m, ArH, 4H), 5.86(s, PyH, 1H), 5.45(s, Py-CH_2, 2H), 2.38(s, CH_3, 3H), 2.34(s, Py-CH_3, 3H), 2.25(s, Py-CH_3, 3H). IR(KBr) ν: 3445 (OH), 3321 (N–H), 1680 (C=O), 1621 (C=N); MS (ESI), *m/z*: 269 (M – 1). Elemental anal. (%), calcd for $C_{15}H_{18}N_4O$: C, 66.64; H, 6.71; N, 20.73; found: C, 66.72; H, 6.35; N, 20.88.

N′-(4-(dimethylamino)benzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl)- acetohydrazide (**4h**): White crystal 91.6% yield; m.p. 203–204 °C; ^{1}H NMR (:DMSO-d_6, 300 MHz), δ 9.25(s, CH, 1H), 8.44(s, NH, 1H), 7.51–7.60(m, ArH, 4H), 5.90(s, PyH, 1H), 5.27(s, Py-CH_2, 2H), 3.03(s, N-CH_3, 3H), 3.01(s, N-CH_3, 3H), 2.28(s, Py-CH_3, 3H), 2.17(s, Py-CH_3, 3H). IR(KBr) ν: 3307 (N–H), 1686 (C=O), 1623 (C=N); MS (ESI), *m/z*: 298 (M – 1), Elemental anal. (%), calcd for $C_{16}H_{21}N_5O$: C, 64.19; H, 7.07; N, 23.39; found: C, 64.44; H, 7.46; N, 23.75.

N′-(2-nitrobenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl) acetohydrazide (**4i**): White crystal 97.5% yield; m.p. 233–234 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 10.00(s, CH, 1H), 8.83(s, NH, 1H), 7.52–8.34(m, ArH, 4H), 5.91(s, PyH, 1H), 5.28(s, Py-CH_2, 2H), 2.29(s, Py-CH_3, 3H), 2.24(s, Py-CH_3, 3H). IR(KBr) ν: 3221 (N–H), 1668 (C=O), 1603 (C=N); MS (ESI), *m/z*: 301 (M – 1). Elemental anal. (%), calcd for $C_{14}H_{15}N_5O_3$: C, 55.81; H, 5.02; N, 23.24; found: C, 55.92; H, 4.89; N, 23.54.

N′-(3-hydroxy-4-methoxy benzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl)acetohydrazide (**4j**): White crystal 92.3% yield; m.p. 161–162 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 7.89(d, *J* = 8.6, ArH, 2H), 7.63(d, *J* = 8.6, ArH, 2H), 7.43–7.55(m, N-PhH, 3H), 7.12(d, *J* = 6.8, N-PhH, 2H), 5.70(s, PyH, 1H), 5.23(s, Py-CH_2, 2H), 4.86(s, S-CH_2, 2H), 2.07 (s, Py-CH_3, 3H), 2.06 (s, Py-CH_3, 3H). IR(KBr) ν: 3209 (N–H), 1680 (C=O), 1619 (C=N); MS (ESI), *m/z*: 301 (M – 1). Elemental anal. (%),calcd for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.00; N, 18.53; found: C, 59.78; H, 6.18; N, 18.52.

N′-(4-fluorobenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl) acetohydrazide (**4k**): White crystal 90.1% yield; m.p. 152–153 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.77(s, CH, 1H), 8.65(s, NH, 1H), 7.29–8.31(m, ArH, 4H), 5.90(s, PyH, 1H), 5.41(s, Py-CH_2, 2H), 2.31(s, Py-CH_3, 3H), 2.25(s, Py-CH_3, 3H). IR(KBr) ν: 3289 (N–H), 1682 (C=O), 1623 (C=N); MS (ESI), *m/z*: 273 (M – 1). Elemental anal. (%), calcd for $C_{14}H_{15}FN_4O$: C, 61.30; H, 5.51; N, 20.43; found: C, 61.34; H, 5.33; N, 20.78.

N′-(4- hydroxybenzylidene)-2-(3,5-dimethyl-1H-pyrazol-1-yl)acetohydrazide (**4l**): White crystal 89.0% yield; m.p. 257–258 °C; ^{1}H NMR ($CDCl_3$, 300 MHz), δ: 9.87(s, CH, 1H), 8.48(s, NH, 1H), 6.94–7.82(m, ArH, 4H), 5.92(s, PyH, 1H), 5.22(s, Py-CH_2, 2H), 2.29(s, Py-CH_3, 3H), 2.26(s, Py-CH_3, 3H). IR(KBr) ν: 3460(OH), 3221 (N–H), 1688 (C=O), 1621 (C=N); MS (ESI), *m/z*: 271 (M – 1), 404. Elemental anal. (%), calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.58; found: C, 61.58; H, 5.62; N, 20.66.

Bioassay of fungicidal activities

Fungicidal activities of some title compounds against *Cladosporium cucumerinum*, *Corynespora cassiicola*, *Sclerotinia sclerotiorum*(Lib.)de Bary, *Erysiphe cichoracearum*, *Colletotrichum orbiculare*(Berk aLMont) Arx. were evaluated using pot culture test according to reference.[14] The culture plates were cultivated at (24±1) °C. The relative inhibition rate of the circle mycelium compared to blank assay was calculated via the following equation:

$$\text{Relative inhibition rate (\%)} = \frac{d_{es} - d_{ex}'}{d_{es}} \times 100\%$$

Where d_{ex} is the extended diameter of the circle mycelium during the blank assay; and d_{ex}', is the extended diameter of the circle mycelium during testing.

Results and discussion

Several procedures are available for the one-step synthesis of hydrazone derivatives. In this paper, several experiments were carried out at various reaction times, power levels, and different ratios of the reactants to establish the optimum reaction conditions. For example the highest yield of compound **4g** was 94.3% at 5 min. But when the time was prolonged, the yield of the compound was decrease. So the best reaction time is 5 min.

Fungicidal activities of title compounds against *Cladosporium cucumerinum*, *Corynespora cassiicola*, *Sclerotinia sclerotiorum* (Lib.)de Bary, *Erysiphe cichoracearum*, *Colletotrichum orbiculare* (Berk aLMont) Arx. were determined. The results were shown in Table **1**. It was also found that some of these compounds displayed excellent fungicidal activity. For example, the biological activity of compound **4a** against *Corynespora cassiicola* and *Colletotrichum orbiculare*(Berk aLMont) Arx. to reach 86.0% and 81.22% respectively. The compound **4e** can inhibit *Erysiphe cichoracearum* to reach 75.14%. The compound **4g** can inhibit *Cladosporium cucumerinum* to reach 60.00%.

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