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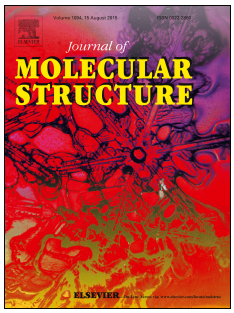


Synthesis, crystal structure, characterization and antifungal activity of 3,4-diaryl-*1H*-Pyrazoles derivatives

Jin Zhang, Da-Jin Tan, Tao Wang, Si-Si Jing, Yang Kang, Zun-Ting Zhang

PII: S0022-2860(17)31050-5

DOI: 10.1016/j.molstruc.2017.07.106

Reference: MOLSTR 24133

To appear in: *Journal of Molecular Structure*

Received Date: 6 April 2017

Revised Date: 28 July 2017

Accepted Date: 29 July 2017

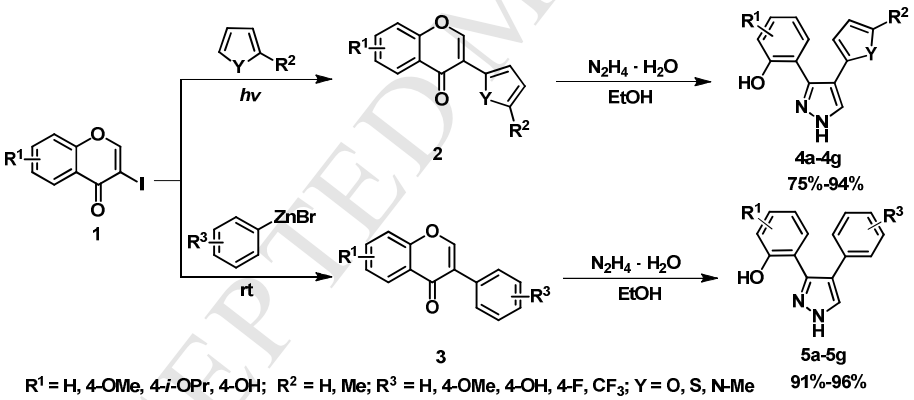
Please cite this article as: J. Zhang, D.-J. Tan, T. Wang, S.-S. Jing, Y. Kang, Z.-T. Zhang, Synthesis, crystal structure, characterization and antifungal activity of 3,4-diaryl-*1H*-Pyrazoles derivatives, *Journal of Molecular Structure* (2017), doi: 10.1016/j.molstruc.2017.07.106.

Graphical abstract:

Synthesis, Crystal Structure, Characterization and Antifungal Activity of Pyrazolo[1,5-*a*]pyrimidines Derivatives

Jin Zhang, Da-Jin Tan, Tao Wang, Si-Si Jing, Yang Kang and Zun-Ting Zhang*

Fourteen 3,4-diaryl-*1H*-pyrazoles (**4** and **5**) derivatives were designed and synthesized by the reaction of chromone with hydrazine hydrate in good yields. The synthesized compounds were characterized by the method of ^{1}H NMR, ^{13}C NMR, IR and HRMS and were evaluated their antifungal properties against five phytopathogenic fungi.



Highlights

- Fourteen 3,4-diaryl-*1H*-pyrazoles (**4** and **5**) derivatives were designed and synthesized by the reaction of chromone with hydrazine hydrate in good yields, and they were characterized by the spectroscopy of ^{1}H NMR, ^{13}C NMR, IR and HRMS.
- The crystal structure of 3-(2,4-dihydroxyphenyl)-4-(4-hydroxyphenyl)-*1H*-pyrazole (**4b**) and 3-(2,4-dihydroxyphenyl)-4-(4-methoxyphenyl)-*1H*-pyrazole (**4c**) was determined.
- The experimental results showed that 3,4-diaryl-*1H*-pyrazoles (**4** and **5**) derivatives existed two tautomeric forms in DMSO-d_6.
- The synthesized compounds were evaluated their antifungal abilities against five phytopathogenic fungi (*Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani* and *Fusarium solani*).

Synthesis, Crystal Structure, Characterization and Antifungal Activity of 3,4-Diaryl-*1H*-Pyrazoles Derivatives

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ABSTRACT

A series of 3,4-diaryl-*1H*-pyrazoles derivatives were designed and synthesized by the reaction of 3-heteroarylchromones and 3-phenylchromones with hydrazine hydrate in good yields. All of those compounds were characterized by ^{1}H NMR, ^{13}C NMR, IR, and HRMS. Moreover, 3-(2,4-dihydroxyphenyl)-4-(4-hydroxyphenyl)-*1H*-pyrazole and 3-(2,4-dihydroxy phenyl)-4-(4-methoxyphenyl)-*1H*-pyrazole were further conformed by the single crystal X-ray diffraction. In addition, the antifungal activity against five phytopathogenic fungi (*Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani* and *Fusarium solani*) of 3,4-diaryl-*1H*-pyrazoles were evaluated. 3-(2-Hydroxy-4-isopropoxyphenyl)-4-phenyl-*1H*-pyrazole was more better and broader inhibitory effect on *Cytospora* sp., *C. gloeosporioides*, *A. solani* and *Fusarium solani* with IC_{50} values of 26.96, 28.84, 16.77 and 22.10 μg/mL, respectively. 4-(4-Fluorophenyl)-3-(2-hydroxy-4-methoxyphenyl)-*1H*-pyrazole exhibited fairly effective antifungal activity against *Cytospora* sp., *C. gloeosporioides* and *A. solani* with IC_{50} values of 11.91, 14.92 and 16.98 μg/mL, respectively.

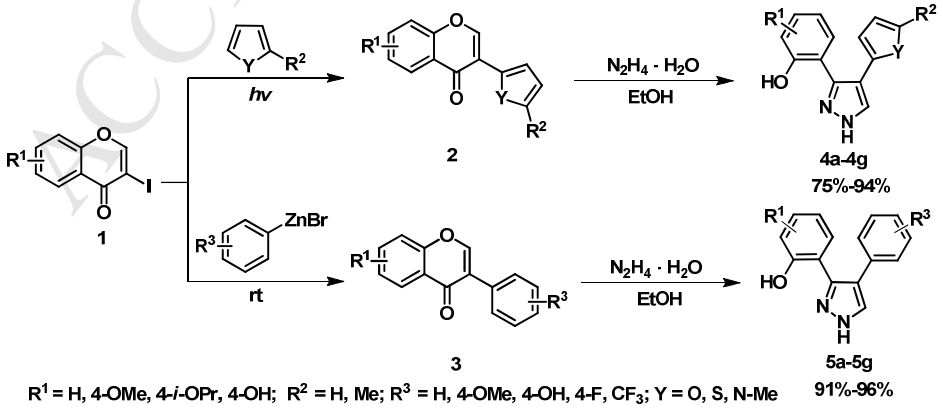
Keywords: 3,4-Diaryl-*1H*-pyrazoles, the single crystal X-ray diffraction, phytopathogens fungi, antifungal activity.

1. Introduction

Pyrazole and its derivatives is a kind of important nitrogenous five-membered heterocyclic compounds, and they are showed unique biological and pharmaceutical activities such as anti-inflammatory [1, 2], antipyretic [3], analgesic [4], antidepressant [5] and antiobesity activity

[6]. In addition, they also can be used as herbizide, insecticide and fungicide [7-9]. Nowadays, many pyrazole derivatives as fungicide have been commercialized, for examples furametpyr and penthiopyrad. Furametpyr has been used to control rice sheath blight in the agriculture field due to it could inhibited the aspirate and glutamate synthesis [10]. Penthiopyrad exhibits activity on strobilurin and DMI resistant diseases, which were caused by powdery mildew, gray mold, rusts, and *Botrytis* [11]. As we all know, phytopathogenic fungi are very hard to control and easily infect many crops [12, 13]. Apart from the yield losses of crop production, phytopathogenic fungi can also be severely harmful to consumers, because they produce dangerous mycotoxins [14, 15].

3,4-Diaryl-*1H*-pyrazoles exhibited antibodies to heat-shock protein 70 and anticancer [16-18]. In our previous work [19], 3,4-diaryl-*1H*-pyrazoles derivatives were synthesized and the antioxidant of them was tested. In 2017, the antifungal activities of 3-arylpyrazoles, 3-aryl-4-halogenatepyrazoles and 2,3-diarylpyrazoles were evaluated by us [20]. It indicated that 3-arylpyrazoles, 3-aryl-4-halogenatepyrazoles and 2,3-diarylpyrazoles showed better and broader spectrum antifungal properties. Based on our previous works [19, 21-22], in this paper, a series of 3,4-diaryl-*1H*-pyrazoles were designed and synthesized (Scheme 1), and their antifungal activities in *vitro* against phytopathogenic fungi *Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani* and *Fusarium solani* were evaluated. In addition, 3-(2,4-dihydroxyphenyl)-4-(4-hydroxyphenyl)-*1H*-pyrazole (**5b**) and 3-(2,4-dihydroxy phenyl)-4-(4-methoxyphenyl)-*1H*-pyrazole (**5c**) were further conformed by the single crystal X-ray diffraction, and other new products were fully characterized by ^{1}H NMR, ^{13}C NMR, IR and HRMS.



Scheme 1. General synthetic route for compounds **4** and **5**.

2. Experimental

2.1.1 Instruments

All starting materials were obtained from commercial sources and used without purification. Melting points were measured using X-5 melting point apparatus and were uncorrected. NMR spectra were recorded on a Bruker AM 400 or 600 instrument using either $CDCl_3$ or DMSO-d_6 as the solvent. The crystal diffraction data were collected on a Bruker Smart-1000 CCD diffractometer. High-resolution mass spectrometry (HRMS) was recorded using electron-spray ionization quadrupole-time of flight (ESI-Q-TOF) technique and IR spectra were recorded on a Nicollet 170SX FT-IR spectrophotometer with KBr pellets. Thin-layer chromatography (TLC) used silica gel 60 GF254 plate. The silica gel (size 200-300 mesh) used for the column chromatography was purchased from Qingdao Haiyang Chemistry Plant (China).

2.1.2 Fungal Materials

Fungi *Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani* and *Fusarium solan* were all kindly provided by the Institute of Pesticides, Northwest A&F University. The strains were inoculated and cultured on potato dextrose agar (PDA) at 28 ± 1 °C for 1 week by the general fungi culture technique [20, 23].

*2.2 General procedure for the synthesis of the intermediates (**2**) and (**3**)*

According to the literature method [24], the intermediate 3-iodochromones (**1**) were prepared. 3-Heteroarylchromones (**2**) were obtained *via* a photochemical reaction with furan, 2-methylfuran, thiophene and 1-*N*-methylpyrrole and 3-iodochromones (**1**) in 60-83% yields [22]. 3-Phenylchromones (**3**) were got *via* the Negishi cross-coupling reactions of aryl zinc reagents and 3-iodochromones (**1**) in 68-81% yields [21, 24].

*2.3 General procedure for the synthesis of 3-phenyl-4-heteroaryl-1H-pyrazoles (**4**) and 3,4-diphenyl-1H-pyrazoles (**5**)*

Compound **2** or **3** (1 mmol) and hydrazine hydrate (2 mmol) were refluxed in ethanol (15 mL) for about 2 h. All reactions were monitored by TLC until the 3-heteroarylchromones was fully consumed. After that the mixture was poured into ice water (100 mL) and was adjusted to pH = 6-7 with 10% HCl. The white precipitate formed was filtered and purified *via* column

chromatography on silica gel (dichloromethane) gave product **4** in 75%-94% yields and **5** in 91%-96% yields. **4a-4g** were new compounds.

*2.3.1. 4-(Furan-2-yl)-3-(2-hydroxyphenyl)-1H-pyrazole (**4a**)*

White solid; mp 123-125 °C; IR (KBr), *v* (cm^{-1}): 3414, 2028, 1625, 1389, 1151, 1075, 750, 622, 482; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 6.39 (m, 1H), 6.46 (m, 1H), 6.84 (m, 1H), 7.05 (d, 1H, *J* = 7.8 Hz), 7.23 (m, 1H), 7.41 (dd, 1H, *J* = 7.8, 1.2 Hz), 7.48 (d, 1H, *J* = 1.2 Hz), 7.77 (s, 1H), 10.33 (br, 2H). ^{13}C NMR (150 MHz, DMSO-d_6) δ(ppm) 108.2, 111.0, 111.2, 116.7, 116.9, 119.5, 128.3, 129.9, 130.7, 141.9, 146.4, 146.7, 155.3. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{13}H_{11}N_2O_2$: 227.0820; found: 227.0824.

*2.3.2. 4-(Furan-2-yl)-3-(2-hydroxy-4-methoxyphenyl)-1H-pyrazole (**4b**)*

Yellow solid; mp 115-117 °C; IR (KBr), *v* (cm^{-1}): 3415, 2028, 1624, 1391, 1283, 1155, 622, 482; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 3.80 (s, 3H, OMe), 6.40 (m, 2H), 6.46 (m, 1H), 6.59 (d, 1H, *J* = 2.4 Hz), 7.28 (m, 1H), 7.47 (d, 1H, *J* = 1.2 Hz), 7.75 (s, 1H), 9.38 (br, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ(ppm) 55.3, 101.8, 106.1, 108.3, 109.6, 110.5, 111.2, 128.9, 130.2, 141.9, 146.4, 147.5, 157.2, 160.9. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{14}H_{13}N_2O_3$: 257.0926; found: 257.0933.

*2.3.3. 3-(2-Hydroxy-4-methoxyphenyl)-4-(5-methylfuran-2-yl)-1H-pyrazole (**4c**)*

Yellow solid; mp 139-141 °C; IR (KBr), *v* (cm^{-1}): 3415, 2028, 1625, 1284, 1160, 1086, 846, 622, 482; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 2.33 (s, 3H), 3.79 (s, 3H), 6.03 (m, 1H), 6.25 (d, 1H, *J* = 2.4 Hz), 6.40 (dd, 1H, *J* = 8.4, 2.4 Hz), 6.58 (d, 1H, *J* = 2.4 Hz), 7.38 (d, 1H, *J* = 8.4 Hz), 7.71 (s, 1H), 9.10 (br, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ(ppm) 13.7, 55.4, 101.8, 106.1, 107.2, 109.2, 109.9, 111.0, 129.1, 130.2, 144.6, 147.2, 151.8, 157.2, 161.0. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{15}H_{15}N_2O_3$: 271.1082; found: 271.1091.

*2.3.4. 3-(2-Hydroxyphenyl)-4-(thiophen-2-yl)-1H-pyrazole (**4d**)*

Yellow solid; mp 143-145 °C; IR (KBr), ν (cm^{-1}): 3460, 3247, 2013, 1616, 1541, 1458, 1377, 1296, 1223, 1016, 974, 822, 760, 611; ^{1}H NMR (600 MHz, $CDCl_3$) δ (ppm) 6.72 (m, 1H), 7.03 (m, 2H), 7.06 (m, 1H), 7.19 (m, 1H), 7.33 (dd, 1H, *J* = 7.8, 1.2 Hz), 7.38 (dd, 1H, *J* = 7.8, 1.2 Hz), 7.65 (s, 1H), 10.47 (br, 2H). HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{13}H_{11}N_2OS$: 243.0592; found: 243.0598. ^{13}C NMR (150 MHz, $CDCl_3$) δ(ppm) 113.3, 116.6, 117.1, 119.4, 125.9, 127.5,

127.7, 128.4, 129.8, 131.1, 133.7, 147.3, 155.7. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{13}H_{11}N_2OS$: 243.0592; found: 243.0598.

*2.3.5. 3-(2-Hydroxy-4-methoxyphenyl)-4-(thiophen-2-yl)-1H-pyrazole (**4e**)*

Yellow solid; mp 117-119 °C; IR (KBr), *v* (cm^{-1}): 3414, 3240, 2028, 1625, 1387, 1199, 1153, 624, 482; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 3.78 (s, 3H), 6.32 (m, 1H), 6.59 (m, 1H), 7.03 (m, 1H), 7.08 (m, 1H), 7.28 (m, 1H), 7.34 (m, 1H), 7.65, 9.95 (br, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ(ppm) 55.4, 102.0, 106.0, 109.8, 112.7, 125.9, 127.6, 129.1, 131.0, 133.9, 147.5, 157.4, 160.9. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{14}H_{13}N_2O_2S$: 273.0697; found: 273.0705.

*2.3.6. 3-(2-Hydroxyphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1H-pyrazole (**4f**)*

Yellow solid; mp 96-98 °C; IR (KBr), *v* (cm^{-1}): 3415, 3240, 2028, 1625, 1392, 1246, 1152, 622, 482; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.26 (s, 3H), 6.20 (dd, *J* = 3.3, 1.8 Hz, 1H), 6.26 (m, 1H), 6.71 (m, 1H), 6.79 (m, 1H), 6.89 (dd, 1H, *J* = 8.1, 1.8 Hz), 7.04 (d, *J* = 8.1 Hz, 1H), 7.18 (m, 1H), 7.63 (s, 1H), 10.83 (br, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ(ppm) 34.2, 108.0, 110.1, 111.1, 116.9, 117.1, 119.7, 123.0, 124.1, 126.7, 129.5, 131.0, 149.2, 156.1. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{14}H_{14}N_3O$: 240.1137; found: 240.1143.

*2.3.7. 3-(2-Hydroxy-4-methoxyphenyl)-4-(1-methyl-1H-pyrrol-2-yl)-1H-pyrazole (**4g**)*

White solid; mp 155-156 °C; IR (KBr), *v* (cm^{-1}): 3415, 2028, 1625, 1392, 1077, 622, 482. ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 3.26 (s, 3H), 3.77 (s, 3H), 6.18 (m, 1H), 6.25 (m, 1H), 6.28 (dd, 1H, *J* = 8.8, 2.6 Hz), 6.57 (d, 1H, *J* = 2.6 Hz), 6.76 (d, 1H, *J* = 8.8 Hz), 6.77 (m, 1H), 7.59 (s, 1H), 10.14 (br, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ(ppm) 34.2, 55.4, 101.9, 106.4, 108.0, 110.2, 110.4, 122.9, 124.2, 127.5, 130.7, 149.5, 157.8, 160.7. HRMS (ESI): m/z $[M + H]^+$ calculated for $C_{15}H_{15}N_3O_2$: 270.1242; found: 270.1243.

*2.3.8. 3-(2-Hydroxyphenyl)-4-phenyl-1H-pyrazole (**5a**)* [25]

White solid; mp 113-115 °C; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 6.80 (s, 1H), 6.01 (s, 1H), 7.09-7.32 (m, 5H), 7.34(d, *J* = 7.3 Hz, 2H), 7.89 (s, 1H), 9.87 (s, 1H), 12.98 (s, 1H). HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{15}H_{13}N_2O$: 237.1028; found: 237.1026.

*2.3.9. 3-(2,4-Dihydroxyphenyl)-4-(4-hydroxyphenyl)-1H-pyrazole (**5b**)* [19]

White solid; mp 252-254 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 6.28 (m, 2H), 6.89 (m, 5H), 7.63 (s, 1H), 9.24-10.50 (m, 3H), 12.55 (s, 1H). HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{15}H_{13}N_2O_3$: 269.0926; found: 269.0921.

*2.3.10. 3-(2,4-Dihydroxyphenyl)-4-(4-methoxyphenyl)-1H-pyrazole (**5c**)* [19]

White solid; mp 210-211; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 3.72 (s, 3H), 6.22 (s, 1H), 6.40 (s, 1H), 6.88 (m, 3H), 7.21 (d, 2H, *J* = 8.4 Hz), 7.70 (s, 1H), 9.48-10.34 (s, 2H), 12.62 (s, 1H). HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{16}H_{14}N_2O_3$: 283.1082; found: 283.1077.

*2.3.11. 3-(2-Hydroxy-4-isopropoxyphenyl)-4-phenyl-1H-pyrazole (**5d**)* [19]

White solid; mp 129-131 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.26 (d, 6H, *J* = 6.0 Hz), 4.54 (m, 1H), 6.36 (s, 1H), 6.46 (s, 1H), 6.99 (d, 1H, *J* = 8.4 Hz), 7.16 (s, 1H), 7.29 (s, 4H), 7.78 (s, 1H), 9.72 (s, 1H), 12.74 (s, 1H). HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{18}H_{19}N_2O_2$: 295.1447; found: 295.1443.

*2.3.12. 3-(2-Hydroxy-4-isopropoxyphenyl)-4-(4-(trifluoromethyl)phenyl)-1H-pyrazole (**5e**)* [26]

White solid; mp 110-112 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.27 (d, 6H, *J* = 5.6 Hz), 4.54 (m, 1H), 6.49 (m, 2H), 7.08 (d, 1H, *J* = 7.5 Hz), 7.51 (d, 2H, *J* = 7.4 Hz), 7.59 (m, 2H), 7.90 (s, 1H), 9.80 (s, 1H), 12.97 (s, 1H). HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{19}H_{18}F_3N_2O_2$: 363.1320; found: 363.1313.

*2.3.13. 3-(2-Hydroxy-4-methoxy-6-methylphenyl)-4-phenyl-1H-pyrazole (**5f**)* [26]

White solid; mp 141-142 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 1.84 (s, 3H), 3.73 (s, 3H), 6.36 (s, 2H), 7.17 (m, 6H), 7.92 (s, 1H), 12.54 (s, 1H). HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{17}H_{17}N_2O_2$: 281.1290; found: 281.1287.

*2.3.14. 4-(4-Fluorophenyl)-3-(2-hydroxy-4-methoxyphenyl)-1H-pyrazole (**5g**)* [26]

White solid; mp 173-175 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ (ppm) 3.72 (s, 3H), 6.41 (d, 1H, *J* = 8.4 Hz), 6.49 (s, 1H), 7.02 (d, 1H, *J* = 8.4 Hz), 7.10 (m, 2H), 7.29 (m, 2H), 7.82 (s, 1H), 9.83 (s, 1H), 12.80 (s, 1H). HRMS (ESI): *m/z* $[M + H]^+$ calculated for $C_{16}H_{14}FN_2O_2$: 285.1039; found: 285.1035.

2.4 Crystal data and structure determination

Data collections for **5b** and **5c** were performed on a Bruker Smart-1000 CCD diffractometer

meter. Both diffractometers were equipped with graphite-monochromated Mo-K*a* radiation (λ = 0.71073 A°) and intensity data for all compounds were collected by the narrow frame method at room temperature. All data sets were corrected for absorption by the *ψ*-*ω* Method. All structures were solved by the direct method and refined by full matrix least-squares fitting on F^2 by SHELX-97. All non-hydrogen atoms were refined anisotropically. All hydrogen atoms were added at calculated position and refined using a riding model. Crystallographic data and structural refinements for **5b** and **5c** were summarized in Table 1.

Table 1.

Crystal and structure refinement data for 5**b** and **5c**.

Crystal Data	**5b**	**5c**
CCDC	886075	1528616
Empirical formula	$C_{15}H_{14}N_2O_4$	$C_{16}H_{14}N_2O_3$
Formula weight	286.28	286.29
Temperature	296(2) K	296(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Hexagonal	Monoclinic
Space group	*R*-3	P2(1)/c
Unit cell dimensions	*a* = 31.4958(12) Å	*a* = 14.6062(16) Å
	b = 31.4958(12) Å	*b* = 7.0612(8) Å
	c = 7.1857(6) Å	*c* = 13.7484(15) Å
	alpha = 90 deg.	alpha = 90 deg.
	beta = 90 deg.	beta = 110.890(2) deg.
	gamma = 120 deg.	gamma = 90 deg.
Volume ($Å^3$)	6173.1(6)	1324.8(3)
Z, Calculated density (mg/m^3)	18, 1.386	4, 1.415
Absorption coefficient (mm^{-1})	0.102	0.099
F (000)	2700	592
Crystal size, mm	0.42 × 0.30 × 0.18	0.46 × 0.29 × 0.24
Theta range for data collection	2.24-25.09 deg.	2.99-25.10 deg.
Limiting indices	-37≤h≤36, -37≤k≤36, -8≤l≤8	-17≤h≤15, -8≤k≤8, -16≤l≤15
Reflections collected / unique	10506 / 2449 [*R*(int) = 0.0285]	6387 / 2366 [*R*(int) = 0.0201]
Completeness to theta	100.0%	99.7%
Max. and min. transmission	0.9816 and 0.9582	0.9765 and 0.9557
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data / restraints / parameters	2449 / 2 / 202	2366 / 0 / 194

Goodness-of-fit on F^2	1.088	1.086
Final *R* indices [*I*>2sigma(*I*)]	*R*1 = 0.0453, *ωR*2 = 0.1277	*R*1 = 0.0407, *ωR*2 = 0.1259
R indices (all data)	*R*1 = 0.0591, *ωR*2 = 0.1375	*R*1 = 0.0485, *ωR*2 = 0.1315
Largest diff. peak and hole	0.556 and −0.515 e.A^{-3}	0.583 and −0.517 e.A^{-3}

2.5 Antifungal Bioassay

According to the literature [22, 23], compounds **4** and **5** were tested for their antifungal performance against five phytopathogenic fungi, such as *Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani*, and *Fusarium solani*. These strains were incubated and cultured on potato dextrose agar (PDA), and prepared in the sterilized Petri dishes to get new mycelium for 7 days at 28 ^{o}C. Then, **4** and **5** dissolved in acetone at the concentrations of 100, 50, 25, 12.5, 6.25 μg/mL and mixed with sterile molten PDA agar medium. Every kind of mycelium was cut to 4.5 mm diameter size and incubated in the center of the dishes on PDA with the sterile conditions at 28 ^{o}C for 4 days. Each sample was performed three times. The commercial fungicide hymexazol and acetone were used as positive control and negative control, respectively. After the mycelia grew completely, the inhibition rate for the mycelia growth was measured using the following formula:

Inhibition rate (%) = (C − T)/(C − 4.5 mm) × 100%

Where C is the average diameter of mycelia in the negative control test, and T is the average diameter of mycelia on other treated PDA.

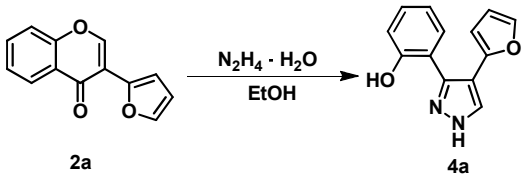
3. Results and discussion

3.1 Chemistry

In our initial investigation, **4a** was prepared according to our previous reports [19, 22-23]. The condensation of 4-furan-3-phenyl-*1H*-pyrazole and hydrazine hydrate in the different solvents such as MeOH, EtOH, MeCN, Hexane, THF, *t*-BuOH and DMF under refluxing were optimized (Table 2). The results showed that the yield of **4a** was the highest (90%) using EtOH as the solvent and refluxing for 2 h.

Table 2.

Solvent effects on the condensation of 4-furan-3-phenyl-*1H*-pyrazole **2a** with hydrazine hydrate[a]



2a 4a

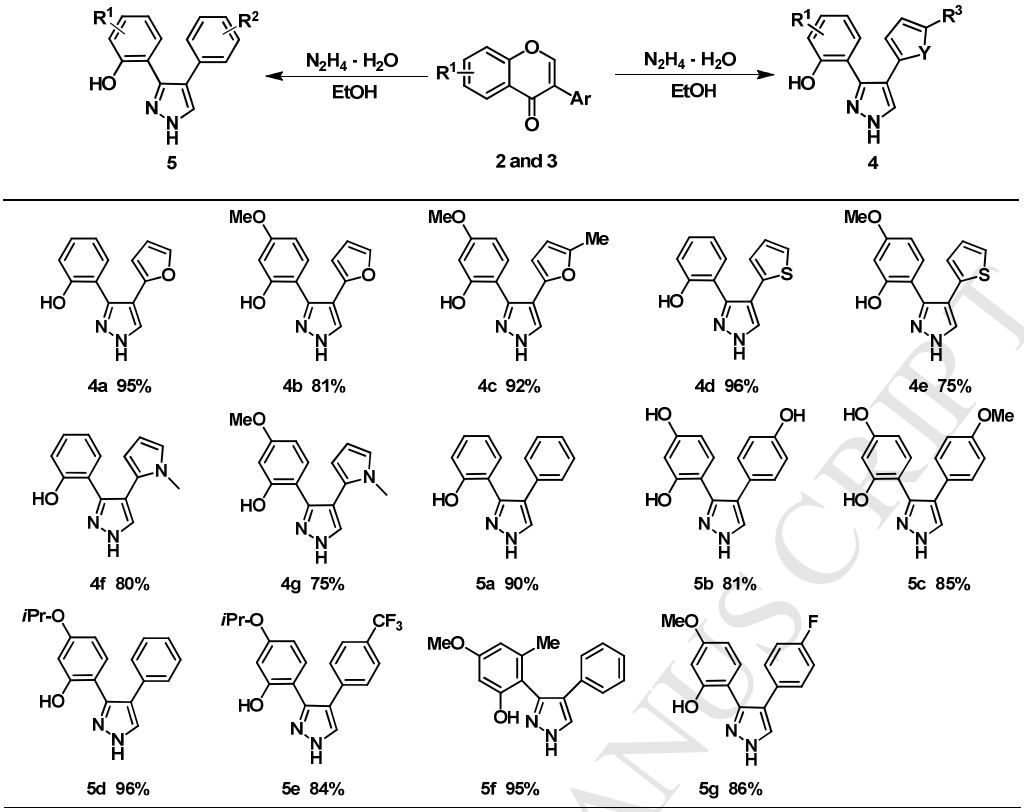
Entry	Solvent	T (^{o}C)	Time (h)	yield (%)[b]
1	CH_3OH	68	3.0	78
2	CH_3CH_2OH	79	2.0	90
3	CH_3CN	80	2.5	65
4	Hexane	69	4.5	58
5	THF	68	4.0	55
6	*t*-BuOH	83	3.0	80
7	DMF	153	1.5	50

[a]All reactions were carried out on 1 mmol scale of **2a** and 2 mmol scale of hydrazine hydrate in 15 mL solvent. Isolated yield on the basis of **2a** and the reaction was monitored by TLC until **2a** was fully consumed.

With the suitable reaction conditions, 3-phenyl-4-heteroaryl-*1H*-pyrazoles (**4**) and 3,4-diphenyl-*1H*-pyrazoles (**5**) were synthesized by the condensation of compound **2** or **3** and hydrazine hydrate. As depicted in Table 3, compound **3** bearing more hydroxyl groups gave the corresponding products in lower yields. For example, product **5a** was obtained in 90% yield, and the yield of **5b** was 81%. When substrates carried electron-donating groups, the corresponding products were obtained in higher yields than those with electron-withdrawing groups. For example, **5g** carried the electron-withdrawing substituent –F, the yield of **4g** (86%, Table 3) was lower than **5f** (95%, Table 3). On the contrary, when a methoxy group was introduced at the *para*-position of the phenyl ring located at 3-position of the pyrazole, the yield of the corresponding product **4** was obviously decreased (**4a** *vs* **4b** and **4d** *vs* **4e**). All new products were fully characterized by ^{1}H NMR, ^{13}C NMR spectra, IR and HRMS.

Table 3.

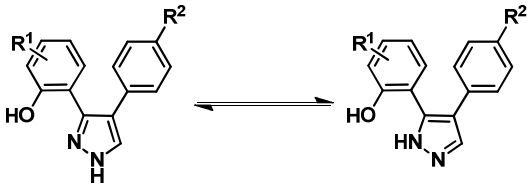
Synthesis of 3-phenyl-4-heteroaryl-*1H*-pyrazoles (**4**) and 3,4-diphenyl-*1H*-pyrazoles (**5**) [a]



[a]All reactions were carried out on 1 mmol scale of compound **2** or **3** and 2 mmol scale of hydrazine hydrate in 15 mL ethanol and monitored by TLC until compound **2** or **3** were fully consumed. Isolated yield on the basis of compound **2** and **3**.

*3.2 Tautomeric forms of 3-phenyl-4-heteroaryl-1H-pyrazoles (**4**) and 3,4-diphenyl-1H-pyrazoles (**5**)*

According to the literature reported [19, 27], compounds **4** and **5** exist in tautomeric forms (Scheme 2). For ^{1}H NMR of **5a**, with DMSO-d_6 as solvent, two neighboring proton peaks at 13.31 ppm and 12.98 ppm were appeared simultaneously in the aromatic region; when D_2O was added to DMSO-d_6, those two proton peaks disappeared and the spectra was simplified *via* the deuterium (^{2}H)-exchange experiments. The experimental results showed that 3,4-diphenyl-*1H*-pyrazoles existed two tautomeric forms at the same time and their integral areas of two proton peaks (12-14 ppm) at N atom have different proportion. For examples, the ratio of tautomers is 4 : 5 in **5a** and 1 : 2 in **5e**. Interestingly, when $CDCl_3$ was as the solvent, compounds **4** and **5** were all absent tautomeric forms and have a single structure.



Scheme 2. Alternative tautomeric forms of **5**.

*3.3 Crystal structure of **5b** and **5c***

The molecular structure of compounds **5b** and **5c** are illustrated in Fig. 1. Single-crystal X-ray diffraction analysis has been performed for the two crystals to determine their structures. The investigations revealed that **5b** and **5c** have a similar structural feature including a pyrazole ring and two phenyl rings. Meanwhile, compound **5b** contains one solvent water molecule and three hydroxyls. Compound **5c** contains a methoxyl group and two hydroxyls. The atom of **5b** and **5c** composed of ring A/B(C1-C6/C10-C15) and pyrazole ring (C7-C9/N1-N2) are not coplanar. The torsion angle of the ring A and pyrazole ring of **5b** and **5c** are 126.4° and 70.9°. The torsion angle of the ring B and pyrazole ring of **5b** and **5c** are 143.0° and 156.0°. To avoid steric conflicts, the dihedral angle between ring A and B of **5b** and **5c** are 129.6° and 76.8°. In the crystal structure of **5c**, the methoxyl groups at C13 is nearly coplanar with its attached ring, indicative of the torsion angle C16-O3-C13-C14 = 7.9°.

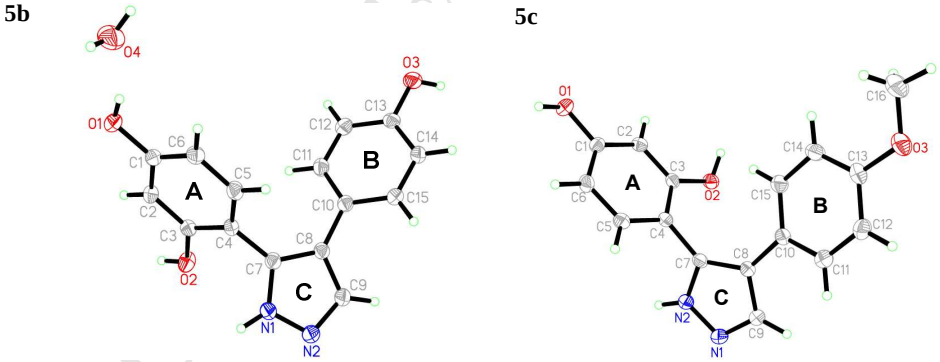


Fig. 1 Molecular structure of **5b** and **5c**

As shown Fig. 2 (a), an obturated center-hollowed ring was generated by 12 hydrogen bonds which formed by six lattice water molecules and six pyrazole skeletons. The bond lengths and angles of O1-H1···O4, O4-H4B···O2$^{(i)}$ [symmetry code (i): x-y+1/3, x-1/3, -z+5/3] were 1.93 Å, 2.00(4) Å and 163.0°, 159(3)°, respectively. Meanwhile, within the obturated center-hollowed ring, a regular hexagon was linked by the six same aromatic hydrogen bonds C15-H15···Cg$^{(ii)}$ with bond length and angle were 2.92 nm and 135°, where the Cg$^{(ii)}$ was the centroid of ring (C10-C15)

at symmetry code (ii): (y+1/3, -x+y+2/3, -z+5/3). The obturated center-hollowed ring was linked into an along ab sheet through hydrogen bonds, which formed by lattice water molecules and other pyrazole skeletons.

Furthermore, Fig. 2 (b) shows how a centrosymmetric dimer is formed through paired N1-H1A…$O^{(i)}$ hydrogen bonds at the inversion position. Within the dimer π–π stacking interactions exist between the two pyrazole skeletons. The two stacking molecules arrange in a centro-symmetric fashion with Cg-$Cg^{(i)}$ = 3.658 Å, where Cg and $Cg^{(i)}$ are the centre of two phenyl ring (C1-C6) of the pyrazole skeleton at (x, y, z) and (1-x, -y, 1-z), respectively. These dimers are linked by aromatic hydrogen bonds C12—H12···$Cg^{(ii)}$ [symmetry code (ii): x, y, 1+z]. Other parts of the four molecules interacted by the same way along axis c. Meanwhile, hydrogen bonds O1—H1···O4, O4—H4B···O4 and O4—H4B···O2 formed by lattice water and lattice water, lattice water and pyrazole skeleton are also existed between the dimmers. Thus, compound **5b** is assembled to a three-dimensional networking structure by hydrogen bonds and aromatic stacking interactions.

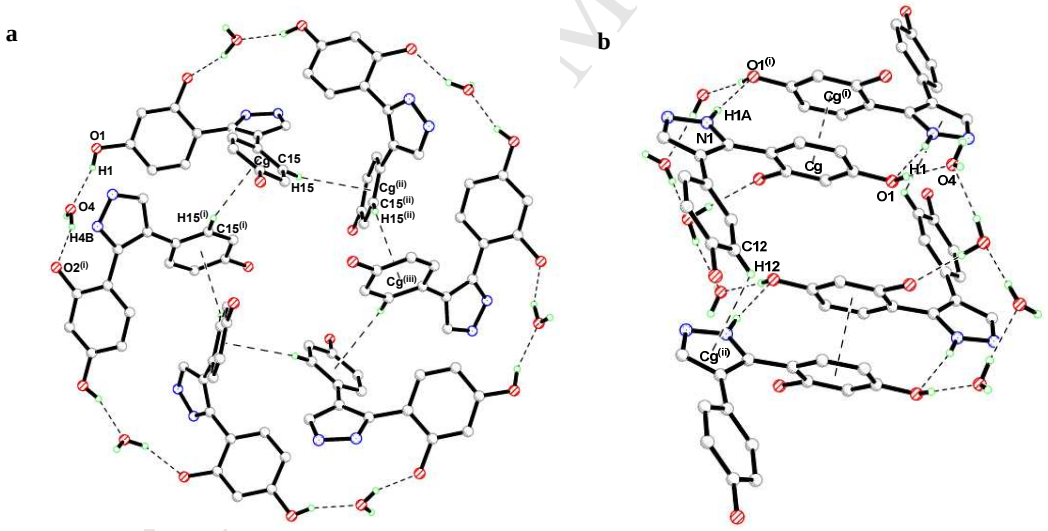


Fig. 2. (a) 2D network of **5b** by C—H···π and H-bonds connections. Symmetry code: (i): x-y+1/3, x-1/3, -z+5/3; (ii): y+1/3, -x+y+2/3, -z+5/3. (b) 3D network of **5b** by C—H···π, H-bonds and π···π connections. Symmetry code: (i): 1-x, -y, 1-z; (ii): x, y, 1+z.

As illustrated in Fig. 3 (a), compound **5c** contains two different C—H···π stackings interaction, and the distances of the H6 to $CgC^{(i)}$ [symmetry code (i): x, 1+y, z] and H16B to $CgA^{(ii)}$ [symmetry code (ii): 1-x, 1-y, 3/2-z] are 2.789 nm and 2.872 nm, which are in the normal range of the C-H···π stacking. Furthermore, two adjacent **5c** molecules also is linked by

$O1^{(iii)}$—$H1^{(iii)}$ ⋯O2 intermolecular hydrogen bonds [symmetry code (iii): x, y-1, z]. Thus, one molecule interacts other three adjacent molecules by intermolecular hydrogen bonds and two different C—H⋯π aromatic hydrogen bonds, and compound **5c** is assembled to a columnar structure along axis-b. In addition, compound **4c** also contains two intermolecular hydrogen bonds (Fig. 3 (b)). Among them, atom N1 and $O1^{(i)}$ acted as acceptor, *via* $H2^{(ii)}$ and H2B, to $O2^{(ii)}$ and N2 from the neighboring molecules, which are observed for $O2^{(ii)}$—$H2^{(ii)}$ ⋯N1 [symmetry code (ii): x, 1/2-y, -1/2+z] and N2—H2B⋯$O1^{(i)}$ [symmetry code (i): -x, 1/2+y, 1/2-z]. The distance of $O2^{(ii)}$ ⋯N1 and N2⋯$O1^{(i)}$ are 2.652 Å and 2.758 Å. The angle of $O2^{(ii)}$—$H2^{(ii)}$ ⋯N1 and N2—H2B…$O1^{(i)}$ are 163° and 153°. (Details of hydrogen bond lengths and angles are given in Table 4). Compound **5c** is assembled to a three-dimensional networking structure by hydrogen bonds and aromatic stacking interactions.

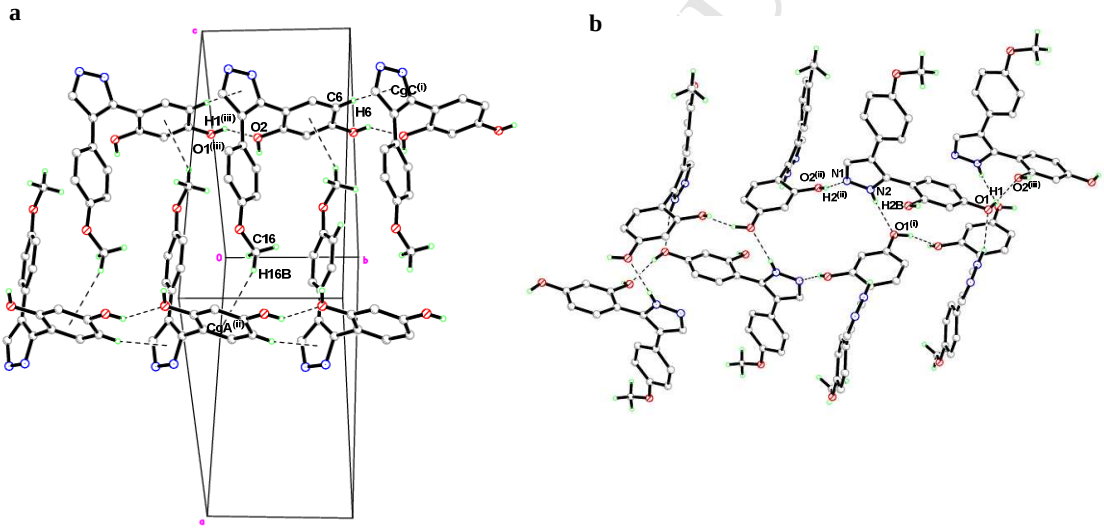


Fig. 3. (a) The C—H···π and H-bonds of compound **5c**. Symmetry code: (i): x, 1+y, z; (ii): 1-x, 1-y, 3/2-z; (iii): x, -1+y, z. (b) Three kinds of hydrogen bonds of **5c**. Symmetry code: (i): -x, 1/2+y, 1/2-z; (ii): x, 1/2-y, -1/2+z; (iii): x, -1+y, z.

Table 4.

Hydrogen bond lengths (Å) and bond angles (°).

D—H···A	D—H	H···A	D—A	∠D—H···A	Symmetric code
5b					
O1—H1…O4	0.82	1.93	2.727 (3)	163	
N1—H1A…O1	0.88	2.12	2.968 (2)	163	2/3-x, 1/3-y, 1/3-z
O2—H2…N2	0.836	1.94	2.752 (4)	167	2/3-x+y, 1/3-x, 1/3+z
O4—H4B…O2	0.84	2.00	2.801 (3)	159	x-y, x, 1-z
O4—H4C…O4	0.84	2.03	2.864 (3)	174	1/3-x+y, 2/3-x, -1/3+z

5c					
O1—H1…O2	0.92	1.91	2.758 (2)	153	x, -1+y, z
O2—H2…N1	0.90	1.78	2.652 (2)	163	x, 1/2-y, -1/2+z
N2—H2B…O1	0.86	2.15	2.957 (2)	155	-x, 1/2+y, 1/2-z

3.4 Antifungal activity

Fourteen 3,4-diaryl-*1H*-pyrazoles derivatives (**4a-4g**, **5a-5g**) were screened for their antifungal activity at a concentration of 100 μg/mL in *vitro* against *Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani*, and *Fusarium solani* (Table 5). Most of those compounds exhibited effectively antifungal performance. Among them, the inhibition rates of compounds **4c-4e**, **4g**, **5a** and **5d-5g** over 70% were selected to obtain their IC_{50} (half-maximal inhibitory concentration) values (Table 6).

Table 5

Preliminary antifungal activities of compounds **4** and **5** at 100 μg/mL[a]

Compd.	Average values of antifungal rate (%)				
	C.s.	C.g.	B.c.	A.s.	F.s.
4a	62.90	68.59	26.45	60.85	46.7
4b	67.02	69.04	31.91	53.59	45.75
4c	68.46	83.11	25.35	77.29	68.38
4d	76.37	92.39	25.96	67.54	87.66
4e	78.76	91.70	31.77	74.45	84.04
4f	37.30	40.31	26.50	33.5	26.74
4g	68.17	74.71	29.05	69.94	70.74
5a	87.36	100	15.87	83.70	89.29
5b	9.30	25.52	2.30	34.01	21.13
5c	69.59	68.6	19.10	63.96	24.53
5d	84.55	74.66	23.20	84.20	80.80
5e	65.32	74.19	15.53	64.46	73.00
5f	93.86	70.71	28.49	76.22	74.7
5g	78.22	88.45	28.03	79.40	29.81
Hy	28.06	38.01	100	55.17	60.1

[a] C.s. *Cytospora* sp.; C.g., *Colletotrichum gloeosporioides*; B.c., *Botrytis cinerea*; A.s. *Alternaria solani*; F.s., *Fusarium solani*; Hy, hymexazol.

As outlined in Table 6, compounds **4** and **5** showed different antifungal activities against the five tested fungi. Most of them exhibited better antifungal activities than the positive control

hymexazol against *Cytospora* sp., *Colletotrichum gloeosporioides*, *Alternaria solani* and *Fusarium solani*. They were all almost inactive against *Botrytis cinerea*.

In case of compounds **4**, **4c** with a methyl group at the *ortho*-position of the furan group showed an effective antifungal activity against *C. gloeosporioides* with IC_{50} values of 29.52 μg/mL. When a thiophene group was introduced to the 4-position of the pyrazole ring, compounds **4d** and **4e** selectively inhibited the growth of *Cytospora* sp. and *C. gloeosporioides*. Especially, **4d** exhibited effective inhibition rate against *C. gloeosporioides* with IC_{50} values of 12.86 μg/mL, which was far more superior to the positive control hymexazol (IC_{50} > 100 μg/mL).

In case of compounds **5**, compound **5a** with a hydroxyl group at the *ortho*-position of the phenyl ring located at 3-position of the pyrazole, showed effective inhibitory activity against *Cytospora* sp. and *C. gloeosporioides* with IC_{50} values of 19.59 and 20.53 μg/mL. When a methoxy group and fluorine atom were simultaneously introduced to the *para*-position of the phenyl ring located at 3- and 4-position of the pyrazole, the antifungal activity and broad-spectrum antifungal property enhanced dramatically. For example, **5g** exhibited fairly good antifungal activity against *Cytospora* sp., *C. gloeosporioides* and *A. solani* with IC_{50} values of 11.91, 14.92 and 16.98 μg/mL, respectively. Moreover, compound **5d**, having a isopropoxy group fixing the *para*-position of the phenyl ring located at 3-position of the pyrazole, was more better and broader inhibitory effect on *Cytospora* sp., *C. gloeosporioides*, *A. solani* and *Fusarium solani* with IC_{50} values of 26.96, 28.84, 16.77 and 22.10 μg/mL, respectively. Compared with our previous work [20], compounds **4c**, **4d**, **4e**, **5d**, and **5g** exhibited better and more selectivity antifungal activities.

Table 6

Antifungal activity of selected compounds

Compd.	IC_{50} ± SD/ (μg/mL)				
	C.s.	C.g.	B.c.	A.s.	F.s.
4c	—	29.52 ± 1.57	—	49.05 ± 2.11	—
4d	36.82 ± 2.86	12.86 ± 6.21	—	—	62.81 ± 0.72
4e	24.87 ± 1.02	30.28 ± 2.49	—	36.71 ± 2.09	53.23 ± 5.19
4g	—	35.36 ± 2.82	—	—	57.73 ± 6.12
5a	19.59 ± 0.89	20.53 ± 1.75	—	35.77 ± 1.47	44.99 ± 6.48
5d	26.96 ± 2.12	28.84 ± 5.39	43.57 ± 2.16	16.77 ± 0.88	22.10 ± 0.43
5e	—	55.13 ± 5.77	—	—	55.31 ± 0.50
5f	37.7 ± 1.56	56.76 ± 4.99	70.37 ± 4.57	41.42 ± 0.54	39.93 ± 3.43

5g	11.91 ± 0.51	14.92 ± 1.14	—	16.98 ± 0.50	—
Hy	>100	>100	7.23 ± 0.33	18.41 ± 0.40	37.42 ± 3.50

[a] — : IC_{50} values was not determined.

4. Conclusions

In summary, we have designed and synthesized fourteen 3,4-diaryl-*1H*-pyrazoles derivatives (**4** and **5**) by the reaction of 3-heteroarylchromones and 3-phenylchromones with hydrazine hydrate in good yields (75-96%). The structure of 3-(2,4-dihydroxyphenyl)-4-(4-hydroxyphenyl)-*1H*-pyrazole (**5b**) and 3-(2,4-dihydroxyphenyl)-4-(4-methoxyphenyl)-*1H*-pyrazole (**5c**) were further conformed by the single crystal X-ray diffraction. Moreover, the antifungal activity of compounds **4** and **5** against phytopathogenic fungi (*Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani* and *Fusarium solani*) were evaluated in *vitro*. The test showed that compounds **4c**, **4d**, **4e**, **5d**, and **5g** exhibited fairly effective antifungal activity against those five phytopathogenic fungi.

Acknowledgements

This research was supported by the National Natural Science Foundation of China (NO. 21672132) and the Fundamental Research Funds for the Central Universities (NO. 2016CBY002).

Abbreviations

HRMS, high resolution mass spectrometry; TLC, thin-layer chromatography; Mp., melting point; IC_{50}, half-maximal inhibitory concentration.

Appendix A. Supplementary data

CCDC 886075 and 1528616 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Center *via* www.ccdc.cam.ac.uk/data_request/cif. HRMS and NMR spectra of compounds **4** and **5**.

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