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Synthesis, crystal structure, characterization and antifungal activity of pyrazolo[1,5-*a*]pyrimidines derivatives

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ABSTRACT

Under microwave radiation, isomers 2-(pyrazolo[1,5-*a*]pyrimidin-5-yl)phenols (**3**) and 2-(pyrazolo[1,5-*a*]pyrimidin-7-yl)phenols (**4**) were simultaneously obtained by the condensation of chromones and 3-aminopyrazoles. These two isomers were fully characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. In addition, a representative product 5-chloro-2-(2-methyl-pyrazolo[1,5-*a*] pyrimidin-5-yl)phenol (**3e**) was further conformed by the single crystal X-ray diffraction. The antifungal abilities of the obtained products **3** and **4** were evaluated against five phytopathogenic fungi (*Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani* and *Fusarium solani*). The results revealed that 2-(pyrazolo[1,5-*a*]pyrimidin-5-yl)phenol (**3a**) and 4-chloro-2-(2-methylpyrazolo[1,5-*a*]pyrimidin-7-yl)phenol (**4e**) exhibited good antifungal abilities against *Colletotrichum gloeosporioides* with the IC_{50} values of 24.90 and 28.28 μg/mL, respectively.

1. Introduction

Pyrazole and pyrimidine derivatives showed a range of diverse pharmacology activities, for instance, anticancer [1], anti-inflammatory [2], protein kinase inhibitors [3], cSRC kinase inhibitors [4], antibacterial [5], or herbicidal, insecticide and fungicidal activities [6,7]. Many fungicidal agents have already been commercialized. Among which pyraclostrobin, rabenzazole and hymexazole were typical representations. Pyraclostrobin was registered for control of leaf diseases and anthracnose fruit rot of straw berry. Rabenzazole was reported to inhibit the synthesis of β-tubulin during mitosis of fungi. Hymexazole was used to against Corticium, *Fusarium*, *Pythium*, *Typhula* spp and *Aphanomyces* [8–10]. It was worth noting that at least 20% losses of food and cash crop was caused by the brown and postharvest disease resulting from the pathogenic fungi [11–16]. Thus, efficient antifungal agent is still urgently desired.

Because of good biological activities of pyrazole and pyrimidine derivatives, we planned to prepare 2-(pyrazolo[1,5-*a*]pyrimidin-7-yl)phenols (**4**) by the condensation of chromens (**1**) and 3-aminopyrazole (**2**) [17–19]. As the conventional heating promoted condensation usually gave the product in low yield after a long reaction time, the microwave radiation was tried. Fortunately, 2-(pyrazolo[1,5-*a*]pyrimidin-5-yl)phenols (**3**) and 2-(pyrazol[1,5-*a*]pyrimidin-7-yl)phenols (**4**) were afforded as two isomers (Scheme 1). In order to distinguish the structure of **3** and **4**, the products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR and HRMS. A representative product 5-chloro-2-(2-methyl-pyrazolo [1,5-*a*] pyrimidin-5-yl)phenol (**3e**) was further conformed by the single crystal X-ray diffraction. The antifungal abilities of prepared **3** and **4** were evaluated against five phytopathogenic fungi (*Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani* and *Fusarium solani*).

2. Experimental

2.1. Instruments

NMR spectra were recorded on a Bruker AM 400 or 600 instrument using either $CDCl_3$ or DMSO-d_6 as the solvent. High-

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

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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. Melting points were measured using X-5 melting point apparatus and were uncorrected. Microwave irradiation was carried out using the commercial microwave oven MCR-3 (Gongyi Yuhua Instrument Corp. Ltd., China). 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).

2.2. Fungal materials

Five types of fungi *Cytospora* sp., *Colletotrichum gloeosporioides*, *Botrytis cinerea*, *Alternaria solani* and *Fusarium solan* were provided by the Institute of Pesticides, Northwest A&F University. The strains were retrieved from the storage tube and cultured on potato dextrose agar (PDA) at 28 °C for 1 week [20].

2.3. General procedure for the synthesis of 2-(pyrazolo[1,5-a]pyrimidin-5-yl)phenols (**3**) and 2-(pyrazolo[1,5-a]pyrimidin-5-yl)phenols (**4**)

Chromone (**1**; 1 mmol), 3-aminopyrazole (**2a**; 1.5 mmol) or 3-amino-5-methyl pyrazole (**2b**; 2 mmol), and CH_3ONa (135 mg, 2.5 mmol) were dissolved in dried DMSO (15 mL). The resulting mixture was heated under microwave irradiation for 10 min at 100 °C. After that the mixture was poured into brine (100 mL) and was adjusted to pH = 6–7 with 20% HCl. The formed precipitate was filtered. Further purified *via* column chromatography on silica gel (dichloromethane) gave product **3** and **4**.

2.3.1. 2-(Pyrazolo[1,5-a]pyrimidin-5-yl)phenol (**3a**)

Yellow solid; mp 153.1–155.5 °C; IR (KBr) ν (cm^{-1}) 3469, 3424, 2027, 1626, 1394, 1075, 623; ^1H NMR (400 MHz, DMSO-d_6) δ (ppm) 12.83 (s, 1H), 9.20 (d, J = 7.6 Hz, 1H), 8.25 (d, J = 2.0 Hz, 1H), 8.09 (d, J = 7.6 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.41 (m, 1H), 7.00 (m, 2H), 6.80 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) δ (ppm) 159.0, 156.8, 145.5, 145.4, 136.7, 132.7, 128.9, 119.3, 118.8, 117.8, 105.5, 95.7. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{12}H_{10}N_3O$: 212.0824; found: 212.0819.

2.3.2. 4-Fluoro-2-(pyrazolo[1,5-a]pyrimidin-5-yl)phenol (**3b**)

Yellow solid; mp 162.4–165.3 °C; IR (KBr) ν (cm^{-1}) 3478, 3417, 2029, 1626, 1420, 1255, 1189, 776, 620; ^1H NMR (600 MHz, $CDCl_3$) δ (ppm) 13.22 (s, 1H), 8.74 (d, J = 7.8 Hz, 1H), 8.15 (d, J = 2.4 Hz, 1H), 7.47 (dd, J = 8.4, 2.4 Hz, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.12 (m, 1H), 7.03 (m, 1H), 6.66 (d, J = 2.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ (ppm) 156.7, 156.4, 155.7 (^1J = 235.2 Hz), 146.0, 145.4, 136.2, 120.2 (^2J = 22.95 Hz), 119.9 (^3J = 7.65 Hz), 117.4 (^3J = 7.2 Hz), 112.9 (^2J = 24.15 Hz), 103.7, 96.4. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{12}H_9FN_3O$: 230.0730; found: 230.0725.

2.3.3. 4-Chloro-2-(pyrazolo[1,5-a]pyrimidin-5-yl)phenol (**3c**)

Yellow solid; mp 168.8–171.4 °C; IR (KBr) ν (cm^{-1}) 3458, 3415, 2965, 2028, 1631, 1406, 1263, 1095, 1025, 804, 626; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.58 (s, 1H), 9.20 (d, J = 7.2 Hz, 1H), 8.26 (d, J = 2.4 Hz, 1H), 8.10 (d, J = 2.4 Hz, 1H), 7.81 (d, J = 7.2 Hz, 1H), 7.42 (dd, J = 2.4, 8.4 Hz, 1H), 7.03 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 2.4 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ(ppm) 157.3, 155.2, 145.6, 145.5, 136.5, 132.0, 128.2, 123.1, 121.0, 119.5, 106.2, 96.1. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{12}H_9ClN_3O$: 246.0434; found: 246.0422.

2.3.4. 5-Methoxy-2-(2-methyl-pyrazolo[1,5-a]pyrimidin-5-yl) phenol (**3d**)

Yellow solid; mp 142.6–145.5 °C; IR (KBr) ν (cm^{-1}) 3456, 3415, 2028, 1622, 1401, 1268, 1157, 844, 636; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 13.58 (s, 1H), 8.99 (d, J = 7.2 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H), 6.57 (dd, J = 8.4, 2.4 Hz, 1H), 6.52 (d, J = 2.4 Hz, 1H), 6.50 (s, 1H), 3.81 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 163.0, 161.5, 156.7, 154.9, 145.3, 136.2, 129.8, 111.2, 106.9, 103.5, 101.8, 94.4, 55.4, 14.2. HRMS (ESI): m/z $[M+Na]^+$ calculated for $C_{14}H_{13}N_3O_2Na$: 278.0905; found: 278.0890.

2.3.5. 5-Chloro-2-(2-methyl-pyrazolo[1,5-a]pyrimidin-5-yl)phenol (**3e**)

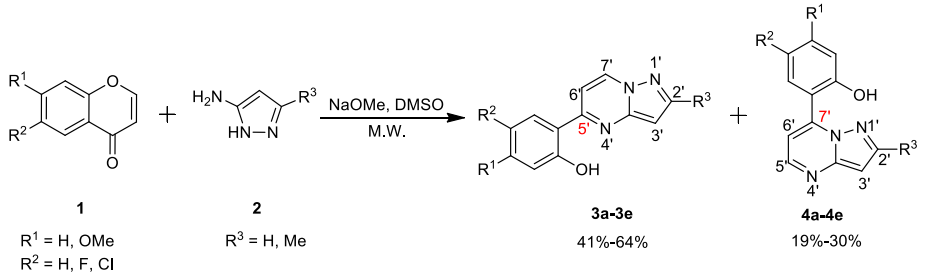
Yellow solid; mp 177.1–179.4 °C; IR (KBr) ν (cm^{-1}) 3465, 3421, 2029, 1625, 1398, 1091, 812, 625; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 12.70 (s, 1H), 9.07 (d, J = 7.8 Hz, 1H), 8.09 (d, J = 2.4 Hz, 1H), 7.72 (d, J = 7.8 Hz, 1H), 7.41 (dd, J = 8.4, 2.4 Hz, 1H), 7.02 (d, J = 8.4 Hz, 1H), 6.60 (s, 1H), 2.44 (s, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 157.4, 155.2, 154.9, 146.2, 136.1, 132.0, 128.1, 123.1, 120.9, 119.6, 105.1, 95.3, 14.3. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{13}H_{11}ClN_3O$: 260.0591; found: 260.0578.

2.3.6. 2-(Pyrazolo[1,5-a]pyrimidin-7-yl)phenol (**4a**)

Yellow solid; mp > 300 °C; IR (KBr) ν (cm^{-1}) 3753, 3463, 3095, 1606, 1539, 1450, 1379, 1271, 1218, 1102, 813, 735; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 10.02 (br, 1H), 8.58 (d, J = 2.4 Hz, 1H), 8.17 (d, J = 2.4 Hz, 1H), 7.54 (d, J = 2.4 Hz, 1H), 7.41 (m, 1H), 7.08 (d, J = 8.4 Hz, 1H), 7.04 (d, J = 8.4 Hz, 1H), 6.97 (m, 1H), 6.79 (d, J = 2.4 Hz, 1H); ^{13}C NMR (150 MHz, DMSO-d_6) δ (ppm) 155.5, 149.0, 148.8, 144.7, 144.0, 131.6, 130.6, 118.8, 118.4, 116.2, 109.3, 96.1. HRMS (ESI): m/z $[M+H]^+$ calculated for $C_{12}H_{10}N_3O$: 212.0824; found: 212.0822.

2.3.7. 4-Fluoro-2-(pyrazolo[1,5-a]pyrimidin-7-yl)phenol (**4b**)

Yellow solid; mp > 300 °C; IR (KBr) ν (cm^{-1}) 3697, 3552, 3410, 3038, 1829, 1597, 1542, 1438, 1380, 1266, 1196, 1121, 880, 781; ^1H NMR (600 MHz, DMSO-d_6) δ (ppm) 10.05 (br, 1H), 8.59 (d,



Scheme 1. General synthetic route for compounds **3** and **4**.