Synthesis and Antifungal Activity of 5-Chloro-6-Phenyl-pyridazin-3(2H)-one Derivatives

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Abstract: An effective method has been developed for the preparation under mild conditions of novel pyridazine derivatives from the easily accessible starting materials mucochloric acid and benzene. All the synthesized compounds were fully characterized and some of them displayed good antifungal activities against G. zeae, F. oxysporum and C. mandshurica in preliminary antifungal activity tests.

Keywords: pyridazine derivatives; synthesis; antifungal activity

1. Introduction

Many pyridazine derivatives are well known to possess a wide range of bioactivities and are often employed as plant virucides [1,2], antitumor agents [3-5], fungicides [6-8], insecticides [9,10], herbicides [11-15] and anti-inflammatory agents [16-17]. They have immense potential in agricultural science as plant growth regulators and crop protection agents. Several derivatives of these compounds incorporating 1,3,4-thiadiazole, 1,3,4-oxadiazole and oxazolidin-2-one rings have been shown to display moderate to good antifungal activities [18-20]. Introduction of methyl N-methoxy-N-[2-(1,6-dihydro-1-substituted-6-oxo-pyridazin-3-ylomethyl) phenyl] carbonate base into pyrazole derived pyraclostrobin has resulted in the development of compounds with appreciable fungicidal activities...
against *P. oryzae*, *B. cinerea* and *E. graminis* [21]. In addition, a series of halogen and aryl substituted pyridazine derivatives synthesized by Akio and Trah [22-23] exhibited high fungicidal activities at a concentration of 50 µg/mL. Since oxadiazole and thiadiazole derivatives are associated with good antifungal characteristics [24-26], we envisioned that modification of 5-chloro-6-phenylpyridazin-3(2H)-one by suitable substituent replacement at the *N*-2 position, followed by incorporation of 1,3,4-thiadiazole and 1,3,4-oxadiazole scaffolds into the pyridazin-3(2H)-one ring through a “-CH<sub>2</sub>S-” moiety could result into the formation of lead structures with potent activity. The pyridazines 3a-3h and 4 without the presence of any oxadiazole and thiadiazole moieties were prepared from mucochloric acid and benzene as depicted in Scheme 1. Then 12 novel pyridazines 6a-6i and 7a-7c derived from 4 incorporating the above structural features were prepared. The synthetic sequence is shown in Scheme 2. All 21 compounds synthesized were unequivocally characterized by IR, NMR and elemental analysis. Preliminary antifungal activity tests showed that most of the compounds exhibited inhibitory activity against *G. zeae*, *F. oxysporum* and *C. mandshurica* to a certain extent. Among them, compounds 3e, 3h, 7b, 7c exhibited slightly superior or similar activities as compared to the commercial agent hymexazol on the corresponding fungi.

**Scheme 1.** Synthetic route to 3a-3h and 4.

**Scheme 2.** Synthetic route to 6a-6i and 7a-7c.
2. Results and Discussion

2.1. Chemistry

3,4-Dichloro-5-phenylfuran-2(5H)-one (1) was synthesized via Friedel-Crafts reaction by employing mucochloric acid and benzene as starting materials in the presence of the Lewis acid AlCl₃, in accordance with the known synthetic protocols described in the literature [27,28].

Preparation of the compound 5-chloro-6-phenylpyridazin-3(2H)-one (2) has been described previously [27,29], but unfortunately in our hands under the same reaction conditions the yield was much lower (46%) compared to the one reported in the literature. It was observed that the type of solvent, reaction temperature and reaction time were the most important parameters affecting the purity and yield of the final product. The best result, affording a yield of 68%, was achieved when the reaction was performed in the solvent DMF at 80°C for 40 min.

5-Chloro-6-phenyl-2-substituted-pyridazin-3(2H)-ones 3a-3h were then conveniently prepared in good yields by treatment of 5-chloro-6-phenylpyridazin-3(2H)-one (2) with halide (XCH₂R, X = Cl or Br) in acetone, acetonitrile or N,N-dimethylformamide. Among these solvents, however, acetone provided the best results and the reaction could be successfully conducted at room temperature. The reaction was much faster and high yielding when X was bromine instead of chlorine. This kind of substitution at the nitrogen atom of 2 in the presence of a base was also previously investigated [28] by Estevez et al.

Compound 2 was also separately reacted (Scheme 1) with paraformaldehyde and thionyl chloride in benzene to afford 5-chloro-2-(chloromethyl)-6-phenylpyridazin-3(2H)-one (4) in a single step in 73% yield. In comparison with the two-step process as reported in the literature [30], the operation was much more convenient and the reaction time was significantly shortened.

Finally, the pyridazine derivatives 6a-6l with 1,3,4-thiadiazole or 1,3,4-oxadiazole moieties were easily obtained in 60-80% yields by the reaction of 5-chloro-2-(chloromethyl)-6-phenylpyridazin-3(2H)-one (4) with 5 as depicted in Scheme 2. As the progress of the reaction was monitored by TLC, the possibility of a side reaction through the chlorine atom at C-5 position of pyrazidine ring could not be ruled out. The reaction time and temperature were critical for this reaction. In general, the products were obtained under mild conditions at 50 °C with a reaction time of 3-4 hours. The compounds 6a-6c were eventually oxidized to 7a-7c by H₂O₂ and (NH₄)₆Mo₇O₂₄ as shown in Scheme 2.

The structures of the compounds 1, 2, 3a-3h, 4, 6a-6i and 7a-7c were established on the basis of their spectroscopic data. The IR spectra showed absorption bands around 3,049-3,099 cm⁻¹ for the Ar-H stretching vibrations and near 1,662-1,678 cm⁻¹ for the presence C=O functional groups. In the ¹H-NMR spectra of the pyridazine derivatives, the 4-H signal appeared as a singlet in 7.14-7.26 ppm range, while the Ar-H peaks of all the derivatives were observed near 6.64-8.40 ppm as a multiplet. The CH₂ peaks were observed as singlets in 5.30-6.31 ppm range.

2.2. Antifungal activity bioassay

The in vitro antifungal screening data of the pyridazine derivatives are provided in Table 1. It was observed that these synthesized compounds showed weak to good antifungal activities against the
tested fungi at 50 μg/mL. Compounds 3d, 3e and 6b were shown to inhibit the growth of *G. zeae* at 45.1%, 43.8%, and 40.4%, respectively; compounds 3d, 3f and 7c exhibited good activities on *F. oxysporum* at 38.2%, 44.2% and 43.1%, respectively while compounds 3d, 3e and 3h inhibited the growth of *C. mandshurica* at 43.5%, 40.6% and 47.8%, respectively. These figures were slightly lower than those of hymexazol. It should be noted that compounds 3h, 7b and 7c showed good activities on *G. zeae* at 50.3%, 57.9% and 60.5%, respectively; compounds 3e and 3h exhibited the growth of *F. oxysporum* at 53.2% and 50.9% respectively and compound 7c exhibited good activity on *C. mandshurica*. Amongst the four compounds 3e, 3h, 7b, 7c that exhibited similar activities as that of hymexazole on their corresponding fungi, the last two showed considerable promise. Although, a definite structure activity relationship could not be established with the limited experimental data and available compounds, it appears that incorporation of oxadiazole or thiadiazole unit through thiol 5 into parent pyridazine derivative and subsequent oxidation of the resulting product to sulfone 7 might have a positive influence to enhance antifungal activity of the designed compounds.

| Compd. (50 μg/mL) | *G. zeae* | *F. oxysporum* | *C. mandshurica* |
|-------------------|-----------|----------------|------------------|
| 3a                | 7.5       | 12.3           | 4.5              |
| 3b                | 8.3       | 18.9           | 19.2             |
| 3c                | 33.7      | 25.5           | 26.7             |
| 3d                | 45.1      | 38.2           | 43.5             |
| 3e                | 43.8      | 53.2           | 40.6             |
| 3f                | 24.2      | 44.2           | 33.8             |
| 3g                | 22.3      | 18.7           | 15.9             |
| 3h                | 50.3      | 50.9           | 47.8             |
| 4                 | 17.8      | 10.7           | 12.1             |
| 6a                | 12.1      | 9.9            | 13.2             |
| 6b                | 40.4      | 27.1           | 30.0             |
| 6c                | 16.2      | 9.4            | 13.8             |
| 6d                | 26.2      | 3.4            | 0.8              |
| 6e                | 29.0      | 9.14           | 1.5              |
| 6f                | 16.6      | 8.1            | 6.2              |
| 6g                | 35.3      | 32.9           | 28.3             |
| 6h                | 11.2      | -3.5           | -2.5             |
| 6i                | 22.1      | 3.8            | 2.0              |
| 7a                | 35.5      | 32.6           | 34.6             |
| 7b                | 57.9      | 35.3           | 26.3             |
| 7c                | 60.5      | 43.1           | 52.1             |
| hymexazol         | 50.4      | 52.4           | 54.1             |

### 3. Experimental

#### 3.1. General

Unless otherwise stated, all the reagents and reactants were purchased from commercial suppliers; melting points were uncorrected and determined on a XT-4 binocular microscope (Beijing Tech
Instrument Co., China). The $^1$H-NMR and $^{13}$C-NMR spectra were recorded on a JEOL ECX 500 NMR spectrometer at room temperature operating at 500 MHz for $^1$H-NMR and 125 MHz for $^{13}$C-NMR, using CDCl$_3$, CD$_3$COCD$_3$ or DMSO as solvents and TMS as an internal standard; infrared spectra were recorded in KBr on a Bruker VECTOR 22 spectrometer; elemental analysis was performed on an Elemental Vario-III CHN analyzer. The course of the reactions was monitored by TLC; analytical TLC was performed on silica gel GF$_{254}$; column chromatographic purification was carried out using silica gel. 5-Subsitituted phenyl-1,3,4-thiadiazoles (or oxadiazole)-2-thiols 5 were prepared according to the literature procedure [25-26] from substituted benzoic acid as the starting material through esterification, hydrazidation, salt formation, and cyclization. All compounds were synthesized under mild conditions with moderate yields.

3.2. Preparation of 3, 4-dichloro-5-phenylfuran-2(5H)-one (1)

Mucoclloric acid (33.0 g) was slowly added with stirring to a mixture of benzene (160 mL) and anhydrous aluminum chloride (40.0 g). After completion of the addition, stirring was continued for 3 h at room temperature. After addition of ice (60.6 g) and conc. HC1 (128 mL), the resulting mixture was extracted with benzene ($4 \times 50$ mL). The combined extract was dried on anhydrous Na$_2$SO$_4$ and concentrated under vacuum to afford a crystalline solid which was filtered off and recrystallized from methanol, m.p. 75-77 °C (lit. [27], m.p. 79-81 °C); yield 60%.

3.3. Preparation of 5-chloro-6-phenylpyridazin-3(2H)-one (2)

Hydrazine hydrate (80%, 6.0 g) was slowly added to a solution of 3,4-dichloro-5- phenylfuran-2(5H)-one (5.0 g) dissolved in N,N-dimethylformamide (30 g). The resulting solution was stirred at 80 °C for 40 min; after cooling, the mixture was added to water (150 mL) to give a precipitate which was filtered off, washed with water and recrystallized from dioxane to give a yellow solid. Yield, 68%; m.p. 231-232 °C (lit. [27], m.p. 230-231°C).

3.4. Preparation of 5-chloro-6-phenyl-2-substitutedpyridazin-3(2H)-ones 3a-3h

To a well stirred solution of 5-chloro-6-phenylpyridazin-3(2H)-one (1.00 mmol) in acetone (8 mL) anhydrous potassium carbonate (0.5 g) and halide (1.00 mmol) were added. The mixture was stirred at room temperature and monitored by TLC. After completion of the reaction, the solid was filtered; the solvent was evaporated and the crude product was purified by preparative TLC with a mixture of petroleum ether and ethyl acetate ($v:v = 1:1$) as developing solvent to give title compounds 3a-3h.

Ethyl 2-(4-chloro-6-oxo-3-phenylpyridazin-1(6H)-yl)acetate (3a): Light yellow solid, yield 72%; m.p. 77.0-78.5 °C; $^1$H-NMR (CDCl$_3$): $\delta$ 7.43-7.57 (m, 5H, Ph-H), 7.16 (s, 1H, pyridazine-H), 4.92 (s, 2H, CH$_2$), 2.25 (q, $J = 7.45$, 2H, CH$_2$), 1.29 (t, $J = 6.9Hz$, 3H, CH$_3$); $^{13}$C-NMR (CDCl$_3$): $\delta$ 167.06, 158.85, 145.82, 140.48, 133.38, 129.73, 129.29, 128.79, 128.35, 62.00, 53.22, 14.21; IR: $\nu$ 3059.1, 3034.0, 2900.0, 1737.8, 1678.0 cm$^{-1}$; Anal. Calc. for C$_{14}$H$_{13}$ClN$_2$O$_3$: C 57.44%, H 4.48%, N 9.57%. Found: C 57.73%, H 4.23%, N 9.98%.
2-(2-Nitrobenzyl)-5-chloro-6-phenylpyridazin-3(2H)-one (3b): White solid, yield 70%, m.p. 116-118 °C; ¹H-NMR (CDCl₃): δ 7.20-8.10 (m, 9H, Ph-H), 7.18 (s, 1H, pyridazine-H), 5.79 (s, 2H, CH₂); ¹³C-NMR (CDCl₃): δ 158.92, 148.65, 146.03, 140.27, 133.75, 133.22, 131.06, 129.80, 129.34, 129.24, 129.04, 128.85, 128.36, 125.36, 152.55; IR: ν 3030.0, 2943.3, 1662.6 cm⁻¹; Anal. Calc. for C₁₇H₁₂ClN₃O₃: C 59.75%, H 3.54%, N 12.30%. Found: C 59.43%, H 3.51%, N 12.02%.

2-(4-Nitrobenzyl)-5-chloro-6-phenylpyridazin-3(2H)-one (3c): White solid, yield 72%, m.p. 143-145 °C; ¹H-NMR (CDCl₃): δ 7.46-8.20 (m, 9H, Ph-H), 7.15 (s, 1H, pyridazine-H), 5.43 (s, 2H, CH₂); ¹³C-NMR (CDCl₃): δ 158.74, 147.86, 145.99, 142.67, 140.24, 133.33, 129.86, 129.78, 129.24, 129.07, 128.42, 124.02, 56.64; IR: ν 3020.0, 2960.1, 1662.6 cm⁻¹; Anal. Calc. for C₁₇H₁₂ClN₃O₃: C 59.75%, H 3.54%, N 12.30%. Found: C 59.85%, H 3.86%, N 12.21%.

5-Chloro-2-[(6-chloropyridin-3-yl)methyl]-6-phenylpyridazin-3(2H)-one (3d): Light yellow solid, yield 68%, m.p. 121-123 °C; ¹H-NMR (acetone-d₆): δ 7.39-8.46 (m, 8H, Ar-H), 7.19 (s, 1H, pyridazine-H), 5.35 (s, 2H, CH₂); ¹³C-NMR (acetone-d₆): δ 158.22, 150.55, 150.11, 145.20, 139.72, 139.47, 134.01, 131.53, 129.45, 129.35, 128.69, 128.20, 124.16, 51.69; IR: ν 3076.4, 3059.1, 2950.0, 1654.9 cm⁻¹; Anal. Calc. for C₁₆H₁₁Cl₂N₃O: C 57.85%, H 3.34%, N 12.65%. Found: C 57.84%, H 3.63%, N 12.14%.

2-(2-Fluorobenzyl)-5-chloro-6-phenylpyridazin-3(2H)-one (3e): White crystals, yield 60%, m.p. 91.7-93.8 °C; ¹H-NMR (CDCl₃): δ 7.05-7.58 (m, 10H, Ar-H), 5.44 (s, 2H, CH₂); ¹³C-NMR (CDCl₃): δ 162.06, 160.08, 158.89, 139.80, 130.80, 130.00, 129.94, 129.61, 129.29, 128.92, 128.31, 124.30, 122.68, 115.75, 115.58, 49.29; IR: ν 3075.0, 3024.3, 1662.6 cm⁻¹; Anal. Calc. for C₁₇H₁₂ClFN₂O: C 64.87%, H 3.84%, N 8.90%. Found: C 64.84%, H 3.80%, N 8.87%.

2-(4-Iodobenzyl)-5-chloro-6-phenylpyridazin-3(2H)-one (3g): White solid, yield 79%, m.p. 75.1-76.9 °C; ¹H-NMR (acetone-d₆): δ 7.21-7.67 (m, 9H, Ph-H), 7.24 (s, 1H, pyridazine-H), 5.28 (s, 2H, CH₂); ¹³C-NMR (acetone-d₆): δ 158.36, 144.47, 139.01, 134.21, 129.39, 129.35, 128.67, 128.63, 128.53, 128.13, 124.50, 110.64, 55.09, 49.75; IR: ν 3061.0, 2953.0, 2833.4 cm⁻¹; Anal. Calc. for C₁₇H₁₂ClN₂O: C 48.31%, H 2.86%, N 6.63%. Found: C 48.63%, H 2.37%, N 6.19%.

2-(2-Methoxybenzyl)-5-chloro-6-phenylpyridazin-3(2H)-one (3h): White solid, yield 70%, m.p. 92.4-94.0 °C; ¹H-NMR (acetone-d₆): δ 7.18 (s, 1H, pyridazine-H), 6.83-7.57 (m, 9H, Ph-H), 5.33 (s, 2H, CH₂), 3.83 (s, 3H, OCH₃); ¹³C-NMR (acetone-d₆): δ 158.36, 157.31, 144.47, 139.01, 134.21, 129.29, 129.31, 128.81, 128.45, 128.13, 124.50, 120.35, 110.64, 55.09, 49.75; IR: ν 3061.0, 2953.0, 2833.4 cm⁻¹; Anal. Calc. for C₁₇H₁₂ClN₂O: C 48.31%, H 2.86%, N 6.63%. Found: C 48.14%, H 2.42%, N 6.36%.
To a round bottomed flask containing dry benzene (50 mL) was added 5-chloro-6-phenylpyridazin-3(2H)-one (4, 2.2 g), paraformaldehyde (1.5 g) and thionyl chloride (3 mL). The resulting mixture was heated under reflux for 1 hour, then cooled to room temperature and filtered. The filtrate was evaporated to dryness under reduced pressure to give a crude solid, which was recrystallised from anhydrous ethanol to afford white crystals, yield 73%, m.p. 108-110 °C; ^1H-NMR (CDCl\textsubscript{3}): δ 7.48-7.59 (m, 6H, Ar-H), 5.86 (s, 2H, CH\textsubscript{2}); ^13C-NMR (CDCl\textsubscript{3}): δ 157.96, 146.92, 141.11, 132.96, 130.06, 129.27, 129.18, 128.45, 57.83; IR: ν 3057.1, 3024.3, 2933.7, 1674.2 cm\textsuperscript{-1}; Anal. Calc. for C\textsubscript{11}H\textsubscript{8}Cl\textsubscript{2}N\textsubscript{2}O: C 51.79%, H 3.16%, N 10.98%. Found: C 51.82%, H 3.24%, N 11.03%.

To a suspension of 5-substituted phenyl-1,3,4-thiadiazole (or oxadiazole)-2-thiol 5 in acetone (or acetonitrile), potassium carbonate (0.5 g) and 5-chloro-2-(chloromethyl)-6-phenylpyridazin-3(2H)-one (4, 2 mmol) were added successively; the mixture was stirred and refluxed for 2 h. The solid was filtered off, and the mother liquor was evaporated to give the crude product, which was purified by chromatography on silica using a mixture of petroleum ether and ethyl acetate (v/v = 2:1) as an eluant to provide the target compounds.

5-Chloro-6-phenyl-2-[[5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-ylthio]methyl]pyridazin-3(2H)-one (6a), White solid, yield 65%, m.p. 97-99 °C; ^1H-NMR (DMSO-d\textsubscript{6}): δ 7.25-7.49 (m, 7H, Ph-H), 7.17 (s, 1H, pyridazine-H), 5.85 (s, 2H, CH\textsubscript{2}), 3.79-3.89 (m, 9H, OCH\textsubscript{3}); ^13C-NMR (DMSO-d\textsubscript{6}): δ 170.68, 166.57, 161.66, 157.64, 157.60, 154.09, 145.25, 140.07, 129.52, 129.21, 128.57, 128.55, 128.13, 128.08, 125.08, 105.18, 104.22, 59.94, 55.91, 55.88, 55.12; IR: ν 3057.1, 3024.4, 2935.7, 2833.4, 1675.1 cm\textsuperscript{-1}; Anal. Calc. for C\textsubscript{22}H\textsubscript{19}ClN\textsubscript{4}O\textsubscript{4}S\textsubscript{2}: C 52.53%, H 3.81%, N 11.14%. Found: C 52.94%, H 3.29%, N 11.62%.

5-Chloro-6-phenyl-2-[(5-phenyl-1,3,4-oxadiazol-2-ylthio)methyl]pyridazin-3(2H)-one (6b): Light yellow solid, yield 75%, m.p. 70.1-71.5 °C; ^1H-NMR (acetone-d\textsubscript{6}): δ 7.32-7.93(m, 10H, Ph-H), 7.22 (s, 1H, pyridazine-H), 5.85 (s, 2H, CH\textsubscript{2}); ^13C-NMR (acetone-d\textsubscript{6}): δ 166.54, 161.58, 157.67, 145.53, 133.53, 132.00, 129.57, 129.29, 129.26, 128.59, 128.15, 126.69, 53.37; IR: ν 3062.9, 3035.9, 2968.4, 1662.6 cm\textsuperscript{-1}; Anal. Calc. for C\textsubscript{19}H\textsubscript{13}ClN\textsubscript{4}O\textsubscript{2}S: C 53.21%, H 3.06%, N 13.06%. Found: C 53.00%, H 3.76%, N 12.64%.

5-Chloro-6-phenyl-2-[[5-(phenyl-1,3,4-thiadiazol-2-ylthio)methyl]pyridazin-3(2H)-one (6c): Light yellow solid, yield 75%, m.p. 87-88 °C; ^1H-NMR (acetone-d\textsubscript{6}): δ 7.34-7.91(m, 10H, Ph-H), 7.23 (s, 1H, pyridazine-H), 5.86 (s, 2H, CH\textsubscript{2}); ^13C-NMR (acetone-d\textsubscript{6}): δ 170.69, 162.06, 157.59, 145.24,
5-Chloro-2-[[5-(2-chlorophenyl)-1,3,4-thiadiazol-2-ylthio]methyl]-6-phenylpyridazin-3(2H)-one (6d): Yellow solid, yield 76%, m.p. 116.9-118.4 °C; ^1H-NMR (DMSO-\(d_6\)) \(\delta\): 7.37-7.68 (m, 10H, Ar-H), 5.87 (s, 2H, CH\(_2\)); ^13C-NMR (DMSO-\(d_6\)) \(\delta\): 165.90, 164.56, 157.99, 145.50, 140.17, 133.53, 133.23, 131.97, 131.25, 131.18, 120.08, 129.54, 129.09, 128.61, 128.36, 55.41; IR: \(\nu\) 3066.8, 3026.3, 2966.5, 1676.1 cm\(^{-1}\); Anal. Calc. for C\(_{19}\)H\(_{12}\)Cl\(_2\)N\(_4\)O\(_2\)S: C 51.01%, H 2.70%, N 12.52%. Found: C 51.49%, H 2.93%, N 12.82%.

5-Chloro-2-[[5-(2-chlorophenyl)-1,3,4-oxadiazol-2-ylthio]methyl]-6-phenylpyridazin-3(2H)-one (6e): Yellow solid, yield 80%, m.p. 112.9-114.7 °C; ^1H-NMR (CDCl\(_3\)) \(\delta\): 7.33-7.87 (m, 9H, Ph-H), 7.14 (s, 1H, pyridazine-H), 5.83 (s, 2H, CH\(_2\)); ^13C-NMR (CDCl\(_3\)) \(\delta\): 165.15, 162.32, 158.13, 146.31, 140.92, 133.22, 132.91, 132.64, 131.33, 131.16, 129.81, 129.18, 128.78, 128.28, 127.14, 122.73, 53.27; IR: \(\nu\) 3061.0, 3041.7, 2980.0, 1678.0 cm\(^{-1}\); Anal. Calc. for C\(_{19}\)H\(_{12}\)Cl\(_2\)N\(_4\)O\(_2\): C 52.91%, H 2.80%, N 12.99%. Found: C 52.41%, H 3.29%, N 12.72%.

5-Chloro-2-[[5-(2-methoxyphenyl)-1,3,4-thiadiazol-2-ylthio]methyl]-6-phenylpyridazin-3(2H)-one (6f): Yellow solid, yield 75%, m.p. 123.6-125.8 °C; ^1H-NMR (CDCl\(_3\)) \(\delta\): 7.14-8.49 (m, 10H, Ar-H), 3.93 (s, 3H, OCH\(_3\)), 5.84 (s, 2H, CH\(_2\)); ^13C-NMR (CDCl\(_3\)) \(\delta\): 164.62, 162.25, 158.19, 155.88, 145.75, 140.62, 133.06, 132.47, 129.64, 129.23, 128.78, 128.44, 128.19, 121.42, 118.96, 111.32, 55.76, 55.25; IR (KBr): \(\nu\) 3061.0, 3041.7, 2980.0, 1670.3 cm\(^{-1}\); Anal. Calc. for C\(_{20}\)H\(_{15}\)ClN\(_4\)O\(_2\)S\(_2\): C 54.23%, H 3.41%, N 12.65%. Found: C 54.81%, H 3.02%, N 12.92%.

5-Chloro-2-[[5-(2-methoxyphenyl)-1,3,4-oxadiazol-2-ylthio]methyl]-6-phenylpyridazin-3(2H)-one (6g): Light yellow solid, yield 70%, m.p. 89.2-90.6 °C; ^1H-NMR (CDCl\(_3\)) \(\delta\): 6.9-7.8 (m, 10H, Ar-H), 3.88 (s, 3H, OCH\(_3\)), 5.80 (s, 2H, CH\(_2\)); ^13C-NMR (CDCl\(_3\)) \(\delta\): 165.63, 161.25, 158.14, 157.90, 146.17, 140.84, 133.39, 132.93, 130.49, 129.74, 129.21, 128.76, 128.25, 120.79, 112.56, 111.95, 56.02, 53.43; IR: \(\nu\) 3070.7, 3034.0, 2983.8, 1664.6 cm\(^{-1}\); Anal. Calc. for C\(_{20}\)H\(_{15}\)ClN\(_4\)O\(_3\)S: C 56.27%, H 3.54%, N 13.12%. Found: C 56.69%, H 3.92%, N 13.60%.

5-Chloro-2-[[5-(2,4-dichlorophenyl)-1,3,4-thiadiazol-2-ylthio]methyl]-6-phenylpyridazin-3(2H)-one (6h): Light yellow crystals, yield 75%, m.p. 142.5-144.1 °C; ^1H-NMR (CDCl\(_3\)) \(\delta\): 7.36-8.26 (m, 8H, Ph-H), 7.14 (s, 1H, pyridazine-H), 5.88 (s, 2H, CH\(_2\)); ^13C-NMR (CDCl\(_3\)) \(\delta\): 164.90, 164.09, 158.20, 146.02, 140.79, 137.53, 133.13, 133.00, 131.65, 130.41, 129.81, 129.20, 128.83, 128.30, 128.04, 127.33, 54.59; IR: \(\nu\) 3068.7, 3022.4, 2953.0, 1674.2 cm\(^{-1}\); Anal. Calc. for C\(_{19}\)H\(_{15}\)Cl\(_3\)N\(_4\)OS\(_2\): C 47.36%, H 2.30%, N 11.63%. Found: C 47.29%, H 2.68%, N 11.30%.

5-Chloro-2-[[5-(2,4-dichlorophenyl)-1,3,4-oxadiazol-2-ylthio]methyl]-6-phenylpyridazin-3(2H)-one (6i): White solid, yield 73%, m.p. 134.5-136.1 °C; ^1H-NMR (DMSO-\(d_6\)) \(\delta\): 7.36-7.93 (m, 9H, Ar-H), 5.87 (s, 2H, CH\(_2\)); ^13C-NMR (DMSO-\(d_6\)) \(\delta\): 163.96, 162.63, 158.04, 145.74, 140.22, 137.82, 133.50,
133.35, 132.75, 131.34, 130.06, 129.52, 129.07, 128.59, 121.44, 53.85; IR: ν 3057.1, 3026.3, 2933.7, 1676.1 cm⁻¹; Anal. Calc. for C_{19}H_{11}Cl_{3}N_{4}O_{2}S: C 49.00%, H 2.38%, N 12.03%. Found: C 48.73%, H 2.69%, N 12.39%.

3.7. Preparation of 5-chloro-6-phenyl-2-[((5-substituted-phenyl)-1,3,4-thiadiazol-2-ylsulfonyl)methyl]pyridazin-3(2H)-ones 7a-7c

To a mixture of compound 6 (1.1 mmol) and ethanol (5 mL) was added 30% H₂O₂ (5.5 mmol) and (NH₄)₆Mo₇O₂₄ (0.011 mmol). The mixture was stirred at 40 °C for 18 h and then filtered off to give a crude product, which was recrystallized from a mixture of anhydrous ethanol and DMF (v/v = 3:1) to afford the desired products.

5-Chloro-6-phenyl-2-[5-(3,4,5-trimethoxyphenyl)-1,3,4-thiadiazol-2-ylsulfonyl)methyl]pyridazin-3(2H)-one (7a): Yellow solid, yield 45%, m.p. 143.3-145.0 °C; ¹H-NMR (CDCl₃): δ 7.11-7.42 (m, 8H, Ar-H), 5.90 (s, 2H, CH₂), 3.94 (s, 9H, CH₃); ¹³C-NMR (CDCl₃): δ 174.34, 165.74, 158.15, 153.86, 147.10, 142.17, 141.28, 132.45, 130.01, 129.07, 129.01, 128.30, 123.66, 105.82, 69.11, 61.23, 56.56; IR: ν 3066.8, 300.2, 2837.6, 2839.2, 1689.6 cm⁻¹; Anal. Calc. for C_{22}H_{19}ClN_{4}O_{6}S_{2}: C 49.39%, H 3.58%, N 10.47%. Found: C 52.94%, H 3.29%, N 11.62%.

5-chloro-6-phenyl-2-[5-(3-phenyl-1,3,4-oxadiazol-2-ylsulfonyl)methyl]pyridazin-3(2H)-one (7b): White solid, yield 55%, m.p. 166-168 °C; ¹H-NMR (DMSO-d₆): δ 7.35-8.00 (m, 11H, Ar-H), 6.31 (s, 2H, CH₂); ¹H-NMR (DMSO-d₆): δ 167.15, 160.93, 158.48, 146.91, 140.80, 133.02, 130.33, 130.14, 129.48, 129.32, 128.65, 128.01, 122.35, 69.39; IR: ν 3095.7, 2999.3, 2914.4, 1672.3 cm⁻¹; Anal. Calc. for C_{19}H_{13}ClN_{4}O_{4}S: C 57.50%, H 3.30%, N 14.14%. Found: C 7.41%, H 3.54%, N 14.64%.

5-chloro-6-phenyl-2-[5-(3-phenyl-1,3,4-thiadiazol-2-ylsulfonyl)methyl]pyridazin-3(2H)-one (7c): White solid, yield 60%, m.p. 154-156 °C; ¹H-NMR (DMSO-d₆): δ 7.37-8.03 (m, 11H, Ar-H), 6.20 (s, 2H, CH₂); ¹³C-NMR (DMSO-d₆): δ 175.00, 166.00, 159.00, 158.26, 147.00, 140.50, 133.48, 133.05, 130.23, 130.12, 129.39, 128.93, 128.60, 69.36; IR: ν 3089.6, 3001.2, 2902.8, 1678.1 cm⁻¹; Anal. Calc. for C_{19}H_{13}ClN_{4}O_{3}S_{2}: C 51.29%, H 2.95%, N 12.59%. Found: C 51.63%, H 2.69%, N 12.92%.

3.8. Antifungal bioassays

The antifungal activity of all synthesized compounds was tested against F. oxysporum, G. zeae, and C. mandshurica by the poison plate technique [31]. All the compounds were dissolved in DMSO (10 mL) before mixing with Potato Dextrose Agar (PDA, 90 mL). The final concentration of the compounds in the medium was fixed at 50 μg/mL. The three kinds of fungi were incubated in PDA at 25 ± 1 °C for 5 days to get new mycelium for the antifungal assays, and then a mycelia disk of approximately 0.45 cm diameter cut from the culture medium was picked up with a sterilized inoculation needle and inoculated in the center of PDA plate. The inoculated plates were incubated at 25 ± 1 °C for 5 days. DMSO in sterilized distilled water served as control, while hymexazole was used as positive control for each treatment with three replicates being conducted for each experiment. The
radial growth of the fungal colonies was measured on the sixth day and the data were statistically analyzed. The in vitro inhibiting effects of the test compounds on the fungi were calculated by the formula $CV = (A - B)/A$, where $A$ represents the diameter of fungi growth on untreated PDA, $B$ represents the diameter of fungi on treated PDA, and $CV$ represents the rate of inhibition.

4. Conclusions

In the present study, a mild and effective method for the preparation of 21 novel pyridazine derivatives were undertaken by employing mucocloric acid and benzene as the starting materials. The synthesized compounds were characterized by spectral data ($^1$H-NMR, $^{13}$C-NMR, IR) and elemental analysis. The compounds were subjected to fungicidal activities in vitro against $G. zeae$, $F. oxysporum$ and $C. mandshurica$. The results showed that the synthesized pyridazine compounds possessed weak to good antifungal activities against the tested fungi, among which, compounds 3e, 3h, 7b, 7c displayed good antifungal activities. Further studies are currently underway to establish a definite structure activity relationship.

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Sample Availability: Samples of the compounds are available from the authors.