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Synthesis of a new series of anti-rhinovirus compounds

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Abstract

The synthesis of a series of 3,6-dichloropyridazine derivatives was described. *In vitro* experiment, all compounds exhibited an anti-rhinovirus activity, and one of the compounds **6g** showed the comparable activity as our lead compound pirodavir.

Keywords: 3,6-Dichoropyridazine derivatives; Synthesis; Anti-rhinovirus

The human rhinovirus (HRV) belongs to the family of picornaviruses and is the main cause for common colds and a variety of other respiratory illnesses, including otitis media, sinusitis, and exacerbations of asthma and reactive airways disease [1]. Inhibitors against rhinovirus have been under active research during the past two decades and several compounds with potent anti-rhinovirus activity have been reported. Pirodavir **1** (Fig. 1), a substituted phenoxypyridazinamine developed by Janssen Research Foundation, was able to decrease rhinovirus infection and reduce the virus shedding in clinical experiment [2]. But the labile ester functional group in the compound prone to rapid hydrolysis to form the corresponding inactive acid losing the clinical benefit [3]. We chose pirodavir as our lead compound and synthesized a series of derivatives with the aim of gaining more effective anti-rhinovirus compounds with better physico-chemical property.

According to docking and virtual screening, we found that chlorine atom substituted in the pyridazine ring could enhance the van der Waals force between the inhibitors and the amino acid residues in the hydrophobic pocket, which was the binding site of the inhibitors. Here we report the synthesis and the anti-rhinovirus activity of a series of 3,6-dichloropyridazine derivatives (Scheme 1).

Compound **3** was obtained in one step according to Refs. [4,5]. Compound **3** (6.54 g, 0.05 mol) dissolved in *N*,*N*-dimethyl acetylamide (10 mL)was added dropwise to the stirred mixture of **2** (9.18 g, 0.05 mol) and anhydrous sodium carbonate (5.30 g, 0.05 mol) in *N*,*N*-dimethyl acetylamide (DMA, 20 mL). The solution was stirred at r.t. overnight, quenched by addition of 100 mL of water and **4** was obtained by filtration [6].

To the stirred and cooled solution of **4** (4 mmol), triphenylposphine (4 mmol) and **5** (4 mmol) in THF (15 mL) was added the solution of diethyl diazenedicarboxylate (4 mmol) in THF (5 mL). After the addition, stirring was continued overnight at r.t. After evaporation, the residue was taken up in water and the product was extracted with dichloromethane. The extract was dried over anhydrous sodium sulfate, evaporated in reduced pressure. The residue

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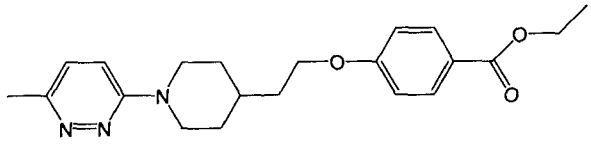
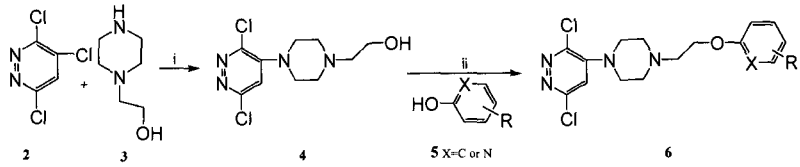


Fig. 1. The structure of Pirodavir **1**.



Scheme 1. (i) Na_2CO_3, DMA, reflux; (ii) Ph_3P, DEAD, THF, reflux. **6a**: X = C, R = 4-CH_2CN; **6b**: X = C, R = 4-NO_2; **6c**: X = C, R = 2-NO_2; **6d**: X = N, R = 4-CO_2CH_3; **6e**: X = C, R = 2-CH_3, 6-CH_3; **6f**: X = C, R = 4-$C(CH_3)_3$; **6g**: X = C, R = 4-OCH_2CH_3.

Table 1
The percentage of cell protection

Compound	Percentage of cell protection (%)
6a	72
6b	32
6c	34
6d	57
6e	60
6f	93
6g	100
Pirodavir	100

was purified by column chromatography on silica gel. The total yield of the two steps was 35–40%. All the compounds of **6a–g** were characterized by EI-MS and ^1H NMR [8].

An assay for cell protection against HRV-3 was used to access the anti-rhinovirus potency of the compounds. All the compounds were dissolved in dimethyl sulfoxide (10 mg/mL) and then diluted with growth medium to achieve the final concentration (100 ng/mL). The dilution of the compounds and the suspension, containing approximately 100 50% tissue culture infective doses ($TCID_{50}$) of HRV-3, was added to tissue culture plate. After half an hour, these virus-compound mixtures were transferred to tissue culture plate with HeLa cells. Plates were incubated for 3 days at 33 °C and checked by light microscopy. When the virus controls showed 100% cytopathic effect (CPE) [7], the percentage of the HeLa cells, which had not shown cytopathic effect (CPE), was calculated to access the ability of cell protection against HRV-3. As shown in Table 1.

Compounds **6a–g** all exhibited anti-rhinovirus activity and compound **6g** showed the comparable activity as the control compound (pirodavir). Further evaluation is still in progress.

Acknowledgments

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[8] **6a**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 7.26–7.24 (m, 2H), 6.93–6.91 (m, 2H), 6.86 (s, 1H), 4.16–4.13 (t, 2H, J = 5.3 Hz), 3.70 (s, 2H), 3.38–3.36 (t, 4H, J = 4.8 Hz), 2.92–2.89 (t, 2H, J = 5.3 Hz), 2.81–2.78 (t, 4H, J = 4.8 Hz); EI-MS (*m/z*, %): 395.0 [M^+ + 4, 1.3], 393.0 [M^+ + 2, 8.4], 391.0 [M^+, 12.0], 259.0 [2.0], 249.0 [23.0], 247.0 [100.0], 245.0 [94.0], 175.1 [24.0]; m.p. (°C): 137–139; Eluent agent (by volume): petroleum:ethyl ether:methanol = 4:4:0.1. **6b**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 8.22–8.20 (d, 2H, J = 9 Hz), 7.40 (s, 1H), 7.20–7.17 (d, 2H, J = 9 Hz), 4.30–4.27 (t, 2H, J = 5.6 Hz), 3.35–3.33 (m, 4H), 2.83–2.81 (t, 2H, J = 5.6 Hz), 2.68–2.66 (m, 4H); EI-MS (*m/z*, %): 399.0 [M^+ + 2, 2.6], 397.0 [M^+, 4.0], 249.0 [12.0], 247.0 [63.0], 245.0 [100.0], 175.0 [7.0]; m.p. (°C): 128–129; Eluent agent (by volume): petroleum:ethyl ether:methanol = 1:0.5:0.1. **6c**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 7.84–7.82 (m, 1H), 7.55–7.54 (m, 1H), 7.11–7.08 (m, 2H), 6.87 (s, 1H), 4.30–4.28 (t, 2H, J = 5.3 Hz), 3.37–3.35 (m, 4H), 2.97–2.95 (t, 2H, J = 5.3 Hz), 2.87–2.85 (m, 4H); EI-MS (*m/z*, %): 396.9 [M^+, 1.2], 379.9 [1.2], 258.9 [7.3], 248.9 [16.0], 246.9 [80.0], 244.9 [100.0], 229.9 [6.2], 175.0 [12.0]; m.p. (°C): 125–126; Eluent agent (by volume): petroleum:ethyl ether:methanol = 8:6:0.3. **6d**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 8.75–8.74 (d, 1H, J = 2.2 Hz), 8.18–8.15 (m, 1H), 7.38 (s, 1H), 6.96–6.94 (d, 1H, J = 8.7 Hz), 4.51–4.48 (t, 2H, J = 5.6 Hz), 3.85 (s, 3H), 3.34–3.33 (m, 4H), 2.80–2.87 (t, 2H, J = 5.6 Hz), 2.66–2.65 (m, 4H); EI-MS (*m/z*, %): 411.1 [M^+, 2.0], 376.1 [3.2], 262.1 [14.3], 260.1 [61.0], 258.1 [92.0], 249.1 [12.0], 247.1 [61.0], 245.1 [100.0], 223.1 [90.0], 180.1 [42.0]; m.p. (°C): 145–146; Eluent agent (by volume): petroleum:ethyl ether:methanol = 10:5:0.2. **6e**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 7.03–7.01 (d, 2H, J = 7.3 Hz), 6.95–6.91 (m, 1H), 6.89 (s, 1H), 3.94(brs, 2H), 3.41 (brs, 4H,), 2.90 (brs, 2H), 2.83 (brs, 4H), 2.29 (s, 6H); EI-MS (*m/z*, %): 382.0 [M^+ + 2, 4.6], 380.0 [M^+, 6.3], 260.9 [8.6], 258.9 [12.0], 249.0 [21.0], 247.0 [100], 245.0 [87.0], 175.0 [15.0]; m.p. (°C): 94–96; Eluent agent (by volume): petroleum:acetone = 6:1. **6f**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 7.32–7.30 (dd, 2H, J_1 = 6.4 Hz, J_2 = 2.0 Hz), 6.86 (s, 1H), 6.87–6.85 (dd, 2H, J_1 = 5.6 Hz, J_2 = 2.4 Hz), 4.15–4.12 (t, 2H, J = 5.6 Hz), 3.37–3.35 (m, 4H), 2.91–2.88 (t, 2H, J = 5.6 Hz), 2.80–2.78 (m, 4H), 1.30 (s, 9H); EI-MS (*m/z*, %): 412.0 [M^+ + 4, 1.6], 410.0 [M^+ + 2, 6.4], 408 [M^+, 8.7], 248.9 [24.0], 246.9 [77.0], 244.9 [100.0], 175.0 [21.0]; m.p. (°C): 97–99; Eluent agent (by volume): petroleum:acetone = 5:1. **6g**: ^{1}H NMR (400 MHz, $CDCl_3$, δ ppm, J Hz): 6.92–6.85 (m, 5H), 4.28 (m, 2H), 4.01–3.96 (q, 2H, J = 7 Hz), 3.53 (brs, 4H), 3.07 (brs, 6H), 1.42–1.38 (t, 3H, J = 7 Hz); EI-MS (*m/z*, %): 400.1 [M^+ + 4, 1.2], 398.1 [M^+ + 2, 8.1], 396.1 [M^+, 10.9], 263.0 [6.0], 261.0 [32.0], 259.0 [52.0], 249.0 [12.0], 247.0 [75.6], 245.0 [100.0], 230.0 [6.0], 175.1 [15.0]; m.p. (°C): 93–95; Eluent agent (by volume): petroleum:ethyl ether:methanol = 10:3:0.5.