Synthesis and characterization of novel N-acyl cyclic urea derivatives

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Abstract
A series of novel N-acyl cyclic urea derivatives (3a-3l) have been synthesized by the reactions of 1-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (1) with various acyl chlorides in the yields of 35-95%. Subsequently, N-acyl cyclic urea derivatives containing α-tertiary amine (5a-5k) have been synthesized by the nucleophilic substitution reaction of 1-(2-haloacetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3e or 3f) with various secondary amines in the yields of 49-86%. The synthesized compounds were characterized by 1H NMR spectroscopy, 13C NMR spectroscopy, high-resolution mass spectroscopy, IR and elemental analysis.

Keywords: Acylation, cyclic urea, N-heterocycles

Introduction

The cyclic urea derivatives have been reported to display a wide range of biological activities, such as the HIV protease inhibitors,1 selective NK1 antagonists,2 Chk1 inhibitors,3 calcium-selective fluoroionophore,4 anti-Alzheimer's disease5 and herbicide.6 Furthermore, cyclic urea derivatives are also used as novel building blocks for bent-core liquid crystals.7 It is noteworthy that N-acyl cyclic urea derivatives are important intermediates in the fields of drugs, pharmaceuticals, polymer materials and chiral auxiliaries for asymmetric synthesis.8-14 The modification of cyclic urea would have the potential to generate new functional molecules, which may result in interesting biological activities.

Heterocyclic compounds, particularly N-heterocycles have attracted attention due to their increasing importance in the fields of pharmaceuticals and agricultural chemicals. For example, various azoles were used clinically as microbicidal agents, antifungal agents and growth inhibitors.15-21 Therefore, to prepare molecules having both N-acyl cyclic urea and N-heterocycles would be a worthwhile programme. These compounds have polyfunctional groups and maybe exhibit multidirectional activity. Based on these facts and in continuation of research on
the application of 1-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (1), here we report the synthesis of novel N-acyl cyclic urea derivatives. The synthetic pathways are depicted in Scheme 1.

Scheme 1. Synthesis of N-acyl cyclic urea derivatives.

Results and Discussion

Table 1. Optimization of N-acylation reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Time/h</th>
<th>Base</th>
<th>Temperature/°C</th>
<th>Isolated yield/%</th>
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<tbody>
<tr>
<td>1</td>
<td>Toluene</td>
<td>22</td>
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<td>30</td>
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<tr>
<td>2</td>
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<td>3</td>
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<td>9</td>
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<td>C_{5}H_{5}N</td>
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<td>80</td>
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<td>Et_{3}N</td>
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<td>THF</td>
<td>1</td>
<td>Et_{3}N</td>
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<td>83</td>
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<td>CH_{2}Cl_{2}</td>
<td>5</td>
<td>Et_{3}N</td>
<td>40</td>
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</tbody>
</table>

Reaction conditions: 1 (5 mmol), benzoyl chloride (2g) (7.5 mmol), base (5 mmol).
Acylation of 1-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (1)
In order to optimize the reaction conditions of N-acylation, we investigated the effects of solvents, times and bases on the reaction of 1 with benzoyl chloride (2g) (Table 1). Initially, the acylation reactions were carried out at different temperature in toluene without any base (entries 1-3). Increasing the temperature from 70 °C to 110 °C could dramatically increase the yield of 1-benzoyl-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3g) in shorter reaction time. In the presence of pyridine (C₅H₅N), the yield of 3g increased significantly to 80% in 4 h (entry 4). In contrast, in the presence of triethylamine (Et₃N), the yield of 3g reached to 89% in 1 h (entry 5). Therefore, Et₃N is more effective for the reaction. Moreover, the effects of solvents such as toluene, THF and CH₂Cl₂ were also studied (entries 5-7). The yields of 3g were 89%, 83% and 78%, respectively. Although 3g had the highest yield when the reaction was conducted in toluene at higher temperature, considering the level of the solvent toxicity, energy-saving, the simplicity of experiment procedure, THF was chosen as solvent for the reaction.

Table 2. Synthesis of N-acyl cyclic urea derivatives 3a-l

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid chloride (2a-2f)</th>
<th>Product</th>
<th>Isolated yield/%</th>
<th>Entry</th>
<th>Acid chloride (2g-2l)</th>
<th>Product</th>
<th>Isolated yield/%</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>O</td>
<td>3a</td>
<td>93</td>
<td>7</td>
<td>O</td>
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<td>91</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>3b</td>
<td>84</td>
<td>8</td>
<td>Cl</td>
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<td>94</td>
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<tr>
<td>3</td>
<td>Cl₅H₅N</td>
<td>3c</td>
<td>89</td>
<td>9</td>
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<td>3iᵇ</td>
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</tr>
<tr>
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<td>O</td>
<td>3d</td>
<td>87</td>
<td>10</td>
<td>N</td>
<td>3jᶜ</td>
<td>53</td>
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<td>5</td>
<td>Cl</td>
<td>3eᵃ</td>
<td>95</td>
<td>11</td>
<td>Cl</td>
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Table 2. Continued

<table>
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<tr>
<th>Entry</th>
<th>Acid chloride (2a-2f)</th>
<th>Product</th>
<th>Isolated yield/%</th>
<th>Entry</th>
<th>Acid chloride (2g-2l)</th>
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<td>3f</td>
<td>89</td>
<td>12</td>
<td>Cl</td>
<td>3l</td>
<td>58</td>
</tr>
</tbody>
</table>

Reaction conditions: 1 (5 mmol), 2a-2l (7.5 mmol), Et₃N (5 mmol), THF (10 mL), reflux.

a Without Et₃N, CH₂Cl₂ (10 mL), room temperature. b toluene (10 mL), reflux. c CH₂Cl₂ (10 mL), reflux.

In a further step, reactions of 1 with various acyl chlorides were carried out in the presence of Et₃N. The results were listed in table 2. The reactions of 1 with various aliphatic acyl chlorides gave N-acyl cyclic urea derivatives 3a-f in excellent yields of 84-95% (entries 1-6). Haloacetyl chlorides reacted with 1 to afford desired products 3e and 3f without any base in the yields of 95% and 89%, respectively (entries 5,6). Analogously, the reactions of 1 and aromatic substituted acyl chlorides also attained 3g-i in 53-94% yields (entries 7-9). As 4-nitrobenzoyl chloride had poorly solubility in THF, toluene was used as solvent to give 3i in moderate yield of 53% (entry 9). Other acyl chlorides (2j-2l) obtained from the reactions of corresponding carboxylic acid and thionyl chloride in-situ also reacted with 1 in CH₂Cl₂ to give 3j-3l in modest yields of 53%, 35% and 58%, respectively (entries 10-12).

Reactions of 1-(2-haloacetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3e, 3f) with secondary amines

With the synthesis of various N-acyl cyclic urea scaffolds established, we turned our attention to assessing the possibility of the N-acyl cyclic urea derivatives 3e or 3f as a scaffold for the synthesis of N-acyl cyclic urea derivatives containing α-tertiary amine groups by the nucleophilic substitution reaction as shown in table 3. In the presence of inorganic base such as anhydrous K₂CO₃ or NaHCO₃, nucleophilic substitution reactions of 3e or 3f and secondary amines were carried out in CH₃CN at reflux temperature. Initially, the reactions of 3e and various N-heterocycles proceeded smoothly to afford 5a-f in the yields of 50-78% (entries 1-6).
Table 3. Synthesis of N-acyl cyclic urea derivatives containing α-tertiary amine groups 5a-l

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine (4a-4f)</th>
<th>Product</th>
<th>Isolated yield/%</th>
<th>Entry</th>
<th>Amine (4g-4l)</th>
<th>Product</th>
<th>Isolated yield/%</th>
</tr>
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<td><img src="image8" alt="Image" /></td>
<td>5j&lt;sup&gt;a,b&lt;/sup&gt;</td>
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<td>5f</td>
<td>61</td>
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<td><img src="image12" alt="Image" /></td>
<td>5l&lt;sup&gt;b&lt;/sup&gt;</td>
<td>90</td>
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</tbody>
</table>

Reaction conditions: 3e (2 mmol), 4a-4l (2-2.4 mmol), NaHCO<sub>3</sub> (2 mmol), CH<sub>3</sub>CN (10 mL), 82 °C. <sup>a</sup> X = Br (3f). <sup>b</sup> K<sub>2</sub>CO<sub>3</sub> as base (1 mmol).

The reactions of 3e or 3f with aliphatic secondary amines gave 5g-j in moderate to good yields (49-86%, entries 7-10). The bulky amines such as dicyclohexylamine and diisopropylamine did not react with 1-(2-chloroacetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3e) smoothly, but they reacted with 1-(2-bromoacetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3f) well to afford 5g and 5j in 49% and 63% yields, respectively (entries 7 and 10). Analogously, the aromatic substituted secondary amine N-methylaniline was reacted with 3e as well to generate 5k in good yield of 72% (entry 11). Interestingly, 3e also reacted with benzothiazole-2-thiol to give 5l in high yield of 90% (entry 12).

Conclusions

We have developed simple and efficient protocols for synthesis of novel N-acyl cyclic urea derivatives. Notably, these compounds have polyfunctional biological active groups and maybe
exhibit multidirectional activity in pharmaceutical and agricultural chemistry.

**Experiment Section**

**General.** All starting materials were obtained commercially and all solvents were dried using standard laboratory procedures. NMR spectra were recorded on a Bruker DRX-500 and DRX-400 NMR spectrometer with CDCl$_3$ as solvent and TMS as internal standard. Mass spectra were recorded on a Waters GCT Premier spectrometer. Elemental analyses were obtained on a Vario EL β. The melting points were determined on an X-4 binocular microscope melting point apparatus and were uncorrected. All reactions were carried out under nitrogen atmosphere.

**General procedure for the synthesis of compounds (3a-l)**

In a 100 mL two necked round bottom flask equipped with a dropping funnel, a condenser and a magnetic stirrer, 1-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (1) (1.06 g, 5 mmol) and Et$_3$N (0.51 g, 5 mmol) in dry THF (10 mL) were stirred under an atmosphere of nitrogen. Then acyl chloride (7.5 mmol) was added dropwise and the reaction mixture was left to stir for 1 h (monitored by TLC) at reflux temperature. The reaction mixture was cooled to room temperature and concentrated under vacuum. The residue was taken up in CH$_2$Cl$_2$ (30 mL) and washed with saturated NaHCO$_3$ (3×20 mL) and brine (20 mL). The organic layer was dried over anhydrous MgSO$_4$. The solvent was evaporated in a rotary evaporator. The residue was washed with anhydrous ether to give the corresponding pure compound.

**1-Acetyl-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3a).** Reaction time: 0.5 h. White solid: 1.18 g (93%). mp 90~91 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 2.53 (s, 3H), 3.34 (t, $J$ 8.0 Hz, 2H), 3.85 (t, $J$ 8.0 Hz, 2H), 4.45 (s, 2H), 7.36 (d, $J$ 8.2 Hz, 1H), 7.65 (dd, $J$ 2.3, 8.2 Hz, 1H), 8.33 (d, $J$ 2.3 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 23.27, 39.34, 40.39, 44.57, 124.61, 130.48, 138.87, 149.12, 151.16, 154.83, 170.52. HRMS calcd for C$_{11}$H$_{12}$ClN$_3$O$_2$: 253.0618; found 253.0616. IR (KBr, cm$^{-1}$): 1728 and 1668 (C=O).

**1-Propionyl-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3b).** Reaction time: 1 h. White solid: 1.12 g (84%). mp 59~60 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 1.17 (t, $J$ 7.4 Hz, 3H), 2.96 (q, $J$ 7.4 Hz, 2H), 3.33 (t, $J$ 8.0 Hz, 2H), 3.85 (t, $J$ 8.0 Hz, 2H), 4.44 (s, 2H), 7.35 (d, $J$ 8.2 Hz, 1H), 7.63 (dd, $J$ 2.3, 8.2 Hz, 1H), 8.32 (d, $J$ 2.3 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 8.56, 28.74, 39.44, 40.49, 44.54, 124.56, 130.49, 138.79, 149.21, 151.21, 154.84, 174.39. Anal. calcd for C$_{12}$H$_{14}$ClN$_3$O$_2$: C 53.84, H 5.27, N 15.70%; found C 53.70, H 5.13, N 15.39%. IR (KBr, cm$^{-1}$): 1728 and 1669 (C=O).

**1-Hexanoyl-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3c).** Reaction time: 1 h. White solid: 1.38 g (89%). mp 44~45 °C. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.90 (t, $J$ 6.9 Hz, 3H), 1.34-1.36 (m, 4H), 1.65-1.68 (m, 2H), 2.94 (t, $J$ 7.6 Hz, 2H), 3.33 (t, $J$ 8.0 Hz, 2H), 3.84 (t, $J$ 8.0 Hz, 2H), 4.44 (s, 2H), 7.35 (d, $J$ 8.2 Hz, 1H), 7.64 (dd, $J$ 2.4, 8.2 Hz, 1H), 8.33 (d, $J$ 2.4 Hz, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 13.87, 22.36, 24.28, 31.37, 35.18, 39.46, 40.46, 44.59, 124.56,
130.50, 138.76, 149.23, 151.26, 154.81, 173.76. HRMS calcd for C_{15}H_{20}ClN_{3}O_{2} 309.1244; found 309.1243. IR (KBr, cm\(^{-1}\)): 1722 and 1672 (C=O).

**1-Isobutyryl-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3d).** Reaction time: 1 h. White solid: 1.22 g (87%). mp 78–79 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.18 (d, \(J = 6.8\) Hz, 6H), 3.33 (t, \(J = 8.0\) Hz, 2H), 3.82-3.90 (m, 3H), 4.45 (s, 2H), 7.35 (d, \(J = 8.2\) Hz, 1H), 7.64 (d, \(J = 8.2\) Hz, 1H), 8.33 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 19.16, 32.39, 39.79, 40.46, 44.70, 124.64, 130.61, 138.87, 149.31, 151.30, 154.58, 178.06. HRMS calcd for C\(_{13}\)H\(_{16}\)ClN\(_3\)O\(_2\) 281.0931; found 281.0932. IR (KBr, cm\(^{-1}\)): 1726 and 1670 (C=O).

**1-(2-Chloroacetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3e).** Reaction time: 1 h. White solid: 1.36 g (95%). mp 115–116 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.41 (t, \(J = 8.0\) Hz, 2H), 3.90 (t, \(J = 8.0\) Hz, 2H), 4.45 (s, 2H), 4.77 (s, 2H), 7.36 (d, \(J = 8.2\) Hz, 1H), 7.63 (d, \(J = 8.2\) Hz, 1H), 8.33 (s, 1H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 39.60, 40.83, 43.33, 44.60, 124.63, 130.02, 138.77, 149.24, 151.43, 154.22, 166.13. Anal. calcd for C\(_{16}\)H\(_{15}\)ClN\(_3\)O\(_2\): C 54.87, H 3.74, N 12.00%; found C 54.79, H 3.76, N 12.01%. IR (KBr, cm\(^{-1}\)): 1727 and 1681 (C=O).

**1-(2-Bromoacetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3f).** Reaction time: 1 h. White solid: 1.47 g (89%). mp 110–111 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 3.40 (t, \(J = 8.0\) Hz, 2H), 3.89 (t, \(J = 8.0\) Hz, 2H), 4.47 (s, 2H), 4.57 (s, 2H), 7.36 (d, \(J = 8.1\) Hz, 1H), 7.64 (d, \(J = 2.4\) Hz, 1H), 8.33 (d, \(J = 2.4\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 27.97, 39.76, 40.56, 44.65, 124.65, 130.04, 138.79, 149.25, 151.45, 154.01, 166.11. HRMS calcd for C\(_{16}\)H\(_{14}\)ClBrN\(_3\)O\(_2\) 330.9723; found 330.9722. IR (KBr, cm\(^{-1}\)): 1726 and 1687 (C=O).

**1-Benzyol-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3g).** Reaction time: 1 h. White solid: 1.43 g (91%). mp 77–78 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 3.42 (t, \(J = 8.0\) Hz, 2H), 4.01 (t, \(J = 8.0\) Hz, 2H), 4.41 (s, 2H), 7.34 (d, \(J = 8.2\) Hz, 1H), 7.43 (t, \(J = 7.5\) Hz, 2H), 7.52 (t, \(J = 7.5\) Hz, 1H), 7.59-7.62 (m, 3H), 8.32 (d, \(J = 2.2\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 40.56, 44.61, 124.60, 127.52, 128.61, 130.48, 131.41, 134.24, 138.83, 149.25, 151.34, 154.25, 170.15. Anal. calcd for C\(_{16}\)H\(_{15}\)ClN\(_3\)O\(_2\): C 60.86, H 4.47, N 13.31%; found C 60.92, H 4.41, N 13.24%. IR (KBr, cm\(^{-1}\)): 1725 and 1689 (C=O).

**1-(4-Chlorobenzoyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3h).** Reaction time: 1 h. White solid: 1.64 g (94%). mp 120–121 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 3.43 (d, \(J = 8.0\) Hz, 2H), 4.00 (t, \(J = 8.0\) Hz, 2H), 4.41 (s, 2H), 7.34 (d, \(J = 8.2\) Hz, 1H), 7.40 (d, \(J = 8.4\) Hz, 2H), 7.55 (d, \(J = 8.4\) Hz, 2H), 7.60 (dd, \(J = 2.3\), 8.2 Hz, 1H), 8.32 (d, \(J = 2.3\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 40.53, 44.61, 126.74, 126.82, 129.30, 130.19, 130.31, 131.79, 132.46, 137.66, 138.82, 149.23, 151.37, 154.13, 169.01. Anal. calcd for C\(_{16}\)H\(_{14}\)ClN\(_3\)O\(_2\): C 54.87, H 3.74, N 12.00%; found C 54.97, H 3.94, N 11.76%. IR (KBr, cm\(^{-1}\)): 1728 and 1665 (C=O).

**1-(4-Nitrobenzoyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3i).** Reaction time: 7 h. White solid: 0.95 g (53%). mp 187–188 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 3.48 (t, \(J = 8.0\) Hz, 2H), 4.05 (t, \(J = 8.0\) Hz, 2H), 4.41 (s, 2H), 7.35 (d, \(J = 8.2\) Hz, 1H), 7.59 (dd, \(J = 2.4\), 8.2 Hz; 1H), 7.72 (d, \(J = 8.7\) Hz, 2H), 8.28 (d, \(J = 8.7\) Hz, 2H), 8.31 (d, \(J = 2.4\) Hz, 1H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 40.27, 40.64, 44.70, 122.87, 124.72, 129.36, 130.01, 138.85, 140.22, 149.13, 149.32, 151.63,
1-Nicotinoyl-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3j). Nicotinic acid (0.62 g, 5 mmol) was added to an over-dried 100 mL round-bottomed flask under N₂. Then thionyl chloride (14 mL) was added. The reaction mixture was heated to 76 °C for 8 h. Then, the excess of thionyl chloride was removed by distillation under vacuum to give nicotinoyl chloride as yellowish-white solid. This crude acyl chloride was dissolved in dry CH₂Cl₂ (10 mL). A solution of 1 (0.42 g, 2 mmol) and dry Et₃N (0.20 g, 2 mmol) in dry CH₂Cl₂ was stirred together at room temperature, under an atmosphere of nitrogen. Then, nicotinoyl chloride was added dropwise and the reaction mixture was left to stir for 1 h (monitored by TLC) at 40 °C. The reaction mixture was added 80 mL saturated NaHCO₃ and extracted with CH₂Cl₂ (3×15 mL). The organic layer were combined, washed with brine (20 mL) and dried over MgSO₄. Solvent evaporation and purification by column chromatography on silica gel (20:1 trichloromethane: methanol) gave white solid of 0.33 g (53%). mp 145~146 oC. ¹H NMR (400 MHz, CDCl₃): δ 3.46 (t, J 7.3 Hz, 2H), 4.04 (t, J 7.3 Hz, 2H), 4.43 (s, 2H), 7.35 (d, J 8.1 Hz, 1H), 7.38 (d, J 5.0 Hz, 1H), 7.62 (d, J 8.1 Hz, 1H), 7.91 (t, J 4.3 Hz, 1H), 8.32 (s, 1H), 8.72 (d, J 3.6 Hz, 1H), 8.82 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 40.41, 40.62, 44.70, 122.41, 124.72, 130.22, 130.27, 136.21, 138.90, 149.31, 149.51, 151.49, 151.86, 154.06, 167.87. Anal. calcd for C₁₆H₁₃ClN₄O₄: C 56.88, H 4.14, N 17.69%; found C 59.17, H 3.74, N 17.68%. IR (KBr, cm⁻¹): 1722 and 1661 (C=O).

1-(4-Chloro-3-ethyl-1-methyl-1H-pyrazole-5-carbonyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3k). In an over-dried 100 mL round-bottomed flask 4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carboxylic acid (0.94 g, 5 mmol) was added under N₂. Then thionyl chloride (14 mL) was added. The reaction mixture was heated to 76 °C for 7 h. The excess of thionyl chloride was removed with a rotary evaporator to give acyl chloride as pale liquid. Then acyl chloride was dissolved in dry CH₂Cl₂ (10 mL). A solution of 1 (0.42 g, 2 mmol) and Et₃N (0.20 g, 2 mmol) in dry CH₂Cl₂ was stirred together at room temperature, under an atmosphere of nitrogen. Subsequently, 4-chloro-3-ethyl-1-methyl-1H-pyrazole-5-carbonyl chloride was added dropwise and the reaction mixture was left to stir for 5 h at 40 °C. The reaction mixture was added 80 mL saturated NaHCO₃ and extracted with DCM (3×15 mL). The organic layer were combined, washed with brine (20 mL) and dried over MgSO₄. Solvent evaporation and purification by column chromatography on silica gel (5:1 ethyl acetate: petroleum ether) gave yellow sticky solid of 0.28 g (35%). mp 145~146 °C. ¹H NMR (400 MHz, CDCl₃): δ 1.26 (t, J 7.5 Hz, 3H), 2.65 (q, J 7.5 Hz, 2H), 3.45 (t, J 7.6 Hz, 2H), 3.89 (s, 3H), 4.01 (t, J 7.6 Hz, 2H), 4.46 (s, 2H), 7.35 (d, J 8.2 Hz, 1H), 7.65 (d, J 8.2 Hz, 1H), 8.32 (s, 1H); ¹³C NMR (100 MHz, CDCl₃): δ 12.78, 19.19, 38.56, 40.27, 40.78, 44.58, 110.03, 124.72, 130.22, 132.98, 138.89, 149.27, 149.65, 151.54, 152.98, 159.16. HRMS calcd for C₁₆H₁₇ClN₅O₂: 381.0759; found 381.0756. IR (KBr, cm⁻¹): 1735 and 1661 (C=O).

(Z)-1-(3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarbonyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3l). (Z)-3-(2-chloro-3,3,3-trifluoroprop-1-enyl)-2,2-dimethylcyclopropanecarboxylic acid (1.21 g, 5 mmol) was added to an over-dried 100
mL round-bottomed flask under N₂. Then thionyl chloride (14 mL) was added. The reaction mixture was heated to 76 °C for 2 h. The excess of thionyl chloride was removed with a rotary evaporator to give corresponding acyl chloride as white solid. Then acyl chloride was dissolved in dry CH₂Cl₂ (10 mL) and placed under N₂. Subsequently, a solution of 1 (0.42 g, 2 mmol) and dry Et₃N (0.20 g, 2 mmol) in dry CH₂Cl₂ (10 mL) was added. The reaction mixture was allowed to stir at 40 °C for 2 h. The reaction mixture was cooled to room temperature, 80 mL saturated NaHCO₃ was added and extracted with DCM (3×15 mL). The organic layer were combined, washed with brine (20 mL) and dried over MgSO₄. Solvent evaporation gave white solid of 0.49 g (58%). mp 131~132 °C.

**1H NMR (400 MHz, CDCl₃):** δ 1.28 (s, 3H), 1.38 (s, 3H), 2.25 (t, J 9.0 Hz, 1H), 3.33 (t, J 8.0 Hz, 2H), 3.59 (d, J 8.4 Hz, 1H), 3.84 (t, J 8.0 Hz, 2H), 4.40-4.52 (m, 2H), 7.03 (d, J 9.6 Hz, 1H), 7.36 (d, J 8.4 Hz, 1H), 7.65 (d, J 8.4 Hz, 1H), 8.34 (s, 1H);

**13C NMR (100 MHz, CDCl₃):** δ 15.18, 28.38, 29.96, 31.93, 33.27, 39.85, 40.36, 44.75, 120.54 (d, J 270.0 Hz, 1C), 120.88 (d, J 37.0 Hz, 1C), 124.68, 130.47, 131.12 (q, J 4.5 Hz, 1C), 138.88, 149.27, 151.37, 155.02, 169.78. HRMS calcd for C₁₈H₁₈Cl₂N₃O₂F₃ 435.0728; found 435.0727. IR (KBr, cm⁻¹): 1709 and 1665 (C=O).

**General procedure for the synthesis of compounds (5a-l)**

In a double-necked round bottomed flask (100 mL) equipped with a condenser, a mixture of an appropriate 4 (2-2.4 mmol) and NaHCO₃ (0.17 g, 2 mmol) or K₂CO₃ (0.14 g, 1 mmol) were dissolved in dry acetonitrile (CH₃CN) (10 mL) and stirred for 1 h at 82 °C under nitrogen atmosphere. Subsequently, 3e (2 mmol, 0.58 g) (3f as substrate was used in the synthesis of 5g and 5j) was added to the mixture and heated at 82 °C for 1-8 h (monitored by TLC). The solvent was evaporated at reduced pressure, then the residue was dissolved in CH₂Cl₂ (40 mL) and washed with H₂O and brine. The organic layer was dried over MgSO₄ and concentrated to afford the crude product, which was purified by column chromatography on SiO₂ eluting with appropriate solvents.

**1-(2-(1H-benzo[d]imidazole-1-yl)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5a).** Base: NaHCO₃. Reaction time: 2 h. The resulting solid was purified by column chromatography using a gradient of 40:1 CH₂Cl₂: CH₃OH to yield white solid of 0.52 g (71%). mp 172~173 °C. **¹H NMR (400 MHz, CDCl₃):** δ 3.37 (t, J 7.7 Hz, 2H), 3.82 (t, J 7.7 Hz, 2H), 4.46 (s, 2H), 5.58 (s, 2H), 7.27-7.30 (m, 2H), 7.36 (d, J 8.1 Hz, 2H), 7.63 (d, J 8.1 Hz, 1H), 7.81 (d, J 6.3 Hz, 1H), 7.97 (s, 1H), 8.34 (s, 1H); **¹³C NMR (100 MHz, CDCl₃):** δ 39.38, 40.97, 44.68, 47.55, 109.60, 120.33, 122.26, 123.18, 124.72, 130.00, 134.35, 138.85, 143.46, 144.07, 149.38, 151.58, 154.60, 166.57. HRMS calcd for C₁₈H₁₈ClN₅O₂ 369.0993; found 369.0995. IR (KBr, cm⁻¹): 1709 and 1665 (C=O).

**1-(2-(1H-imidazole-1-yl)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5b).** Base: NaHCO₃. Reaction time: 3 h. White solid: 0.32 g (50%). mp 122~123 °C. **¹H NMR (400 MHz, CDCl₃):** δ 3.43 (t, J 7.5 Hz, 2H), 3.87 (t, J 7.5 Hz, 2H), 4.47 (s, 2H), 5.37 (s, 2H), 6.96 (s, 1H), 7.09 (s, 1H), 7.37 (d, J 7.9 Hz, 1H), 7.52 (s, 1H), 7.64 (d, J 7.9 Hz, 1H), 8.34 (s, 1H); **¹³C NMR (100 MHz, CDCl₃):** δ 39.41, 41.00, 44.68, 49.55, 120.35, 124.72, 129.30, 130.01, 138.28,
138.84, 149.36, 151.57, 154.53, 166.94. HRMS calcd for C_{14}H_{14}ClN_{5}O_{2} 319.0836; found 319.0837. IR (KBr, cm\(^{-1}\)): 1722 and 1687 (C=O).

1-(2-(1H-benzo[d][1,2,3]triazol-1-yl)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5c). Base: NaHCO\(_3\). Reaction time: 2 h. The resulting solid was purified by column chromatography using a gradient of 40:1 CH\(_2\)Cl\(_2\): CH\(_3\)OH to yield white solid of 0.43 g (58%). mp 185–186 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.43 (t, \(J\ 7.6\ Hz, 2\ H\)), 3.86 (t, \(J\ 7.6\ Hz, 2\ H\)), 4.49 (s, 2H), 6.09 (s, 2H), 7.38 (d, \(J\ 7.7\ Hz, 2\ H\)), 7.44-7.51 (m, 2H), 7.67 (d, \(J\ 7.7\ Hz, 1\ H\)), 8.08 (d, \(J\ 8.2\ Hz, 1\ H\)), 8.36 (s, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 39.34, 41.15, 44.66, 50.95, 109.47, 120.01, 123.97, 124.75, 127.74, 130.07, 133.96, 138.93, 145.91, 149.39, 151.53, 154.68, 165.72. HRMS calcd for C\(_{17}\)H\(_{15}\)ClN\(_6\)O\(_2\) 370.0945; found 370.0944. IR (KBr, cm\(^{-1}\)): 1722 and 1687 (C=O).

1-(2-Morpholinoacetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5d). Base: NaHCO\(_3\). Reaction time: 1 h. White solid: 0.49 g (72%). mp 117–118 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 2.65 (s, 4H), 3.37 (t, \(J\ 7.8\ Hz, 2\ H\)), 3.78-3.87 (m, 8H), 4.43 (s, 2H), 7.36 (d, \(J\ 7.9\ Hz, 1\ H\)), 7.63 (d, \(J\ 7.9\ Hz, 1\ H\)), 8.33 (s, 1H); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 39.23, 40.89, 44.66, 53.87, 60.97, 66.85, 124.64, 130.33, 138.80, 149.31, 151.42, 154.68, 169.91. HRMS calcd for C\(_{15}\)H\(_{19}\)ClN\(_4\)O\(_3\) 338.1146; found 338.1149. IR (KBr, cm\(^{-1}\)): 1726 and 1674 (C=O).

1-(2-(Piperidin-1-yl)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5e). Base: NaHCO\(_3\). Reaction time: 3 h. White solid: 0.52 g (78%). mp 98–99 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.42-1.47 (m, 2H), 1.62-1.66 (m, 4H), 2.57 (t, \(J\ 5.6\ Hz, 4\ H\)), 3.35 (t, \(J\ 8.1\ Hz, 2\ H\)), 3.79 (s, 2H), 3.84 (t, \(J\ 8.1\ Hz, 2\ H\)), 4.42 (s, 2H), 7.35 (d, \(J\ 8.2\ Hz, 1\ H\)), 7.63 (dd, \(J\ 2.4, 8.2\ Hz, 1\ H\)), 8.32 (d, \(J\ 2.4\ Hz, 1\ H\)); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 23.93, 25.75, 39.15, 40.78, 44.55, 54.74, 61.37, 124.54, 130.34, 138.73, 149.20, 151.25, 154.68, 170.44. HRMS calcd for C\(_{16}\)H\(_{21}\)ClN\(_4\)O\(_2\) 336.1353; found 336.1352. IR (KBr, cm\(^{-1}\)): 1709 and 1678 (C=O).

1-(2-(Pyrrolidin-1-yl)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5f). Base: NaHCO\(_3\). Reaction time: 1 h. White solid: 0.39 g (61%). mp 92–93 °C. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 1.82-1.85 (m, 4H), 2.72 (t, \(J\ 6.6\ Hz, 4\ H\)), 3.36 (t, \(J\ 8.1\ Hz, 2\ H\)), 3.86 (t, \(J\ 8.1\ Hz, 2\ H\)), 3.97 (s, 2H), 4.42 (s, 2H), 7.35 (d, \(J\ 8.2\ Hz, 1\ H\)), 7.63 (dd, \(J\ 2.4, 8.2\ Hz, 1\ H\)), 8.32 (d, \(J\ 2.4\ Hz, 1\ H\)); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 23.65, 39.20, 40.86, 44.61, 54.33, 58.68, 124.60, 130.36, 138.78, 149.26, 151.36, 154.76, 170.63. HRMS calcd for C\(_{15}\)H\(_{19}\)ClN\(_4\)O\(_2\) 322.1197; found 322.1196. IR (KBr, cm\(^{-1}\)): 1735 and 1687 (C=O).

1-(2-(Dicyclohexylamino)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5g). Base: K\(_2\)CO\(_3\). Reaction time: 6.5 h. The resulting solid was purified by column chromatography using a gradient of 30:1 CH\(_2\)Cl\(_2\): CH\(_3\)OH to give yellow oil of 0.42 g (49%). \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 1.18-1.20 (m, 9H), 1.57-1.60 (m, 2H), 1.73-1.79 (m, 9H), 2.64-2.68 (m, 2H), 3.35 (t, \(J\ 7.6\ Hz, 2\ H\)), 3.84 (t, \(J\ 7.6\ Hz, 2\ H\)), 4.00 (s, 2H), 4.43 (s, 2H), 7.35 (d, \(J\ 8.0\ Hz, 1\ H\)), 7.65 (d, \(J\ 8.0\ Hz, 1\ H\)), 8.34 (s, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 26.06, 26.13, 31.57, 39.45, 40.96, 44.60, 50.49, 58.69, 124.53, 130.50, 138.75, 149.24, 151.24, 155.16, 174.54. HRMS calcd for C\(_{23}\)H\(_{33}\)ClN\(_5\)O\(_2\) 432.2292; found 432.2292. IR (KBr, cm\(^{-1}\)): 1722 and 1687 (C=O).
1-(2-(Diethylamino)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5h). Base: NaHCO₃. Reaction time: 1.5 h. Yellow oil: 0.45 g (69%). ¹H NMR (500 MHz, CDCl₃): δ 1.07 (t, J 7.2 Hz, 6H), 2.71 (q, J 7.2 Hz, 4H), 3.36 (t, J 8.1 Hz, 2H), 3.85 (t, J 8.1 Hz, 2H), 3.94 (s, 2H), 4.43 (s, 2H), 7.35 (d, J 8.2 Hz, 1H), 7.64 (dd, J 2.4, 8.2 Hz, 1H), 8.33 (d, J 2.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 12.04, 39.17, 40.82, 44.55, 47.58, 55.57, 124.53, 130.36, 138.73, 149.20, 151.25, 154.78, 171.66. HRMS calcld for C₁₅H₂₁ClN₄O₂ 324.1353; found 324.1354. IR (KBr, cm⁻¹): 1722 and 1691 (C=O).

1-(2-(Diisobutlamino)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5i). Base: NaHCO₃. Reaction time: 5.5 h. Yellow oil: 0.65 g (86%); ¹H NMR (500 MHz, CDCl₃): δ 0.88 (d, J 6.6 Hz, 12H), 1.64-1.70 (m, 2H), 2.41 (d, J 7.2 Hz, 4H), 3.34 (t, J 8.1 Hz, 2H), 3.82 (t, J 8.1 Hz, 2H), 3.98 (s, 2H), 4.41 (s, 2H), 7.34 (d, J 8.2 Hz, 1H), 7.62 (dd, J 2.2, 8.2 Hz, 1H), 8.32 (d, J 2.2 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 20.63, 27.08, 38.96, 40.97, 44.62, 57.21, 63.37, 124.59, 130.47, 138.81, 149.26, 151.32, 154.94, 172.62. HRMS calcld for C₁₉H₂₉ClN₄O₂ 380.1979; found 380.1980. IR (KBr, cm⁻¹): 1722 and 1683 (C=O).

1-(2-(Diisopropylamino)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5j). Base: K₂CO₃. Reaction time: 8 h. The resulting solid was purified by column chromatography using a gradient of 30: 1 CH₂Cl₂: CH₃OH to afford yellow oil of 0.44 g (63%). ¹H NMR (500 MHz, CDCl₃): δ 1.05 (d, J 6.3 Hz, 12H), 3.14 (s, 2H), 3.36 (t, J 8.1 Hz, 2H), 3.85 (t, J 8.1 Hz, 2H), 3.93 (s, 2H), 4.44 (s, 2H), 7.36 (d, J 8.2 Hz, 1H), 7.65 (dd, J 2.2, 8.2 Hz, 1H), 8.31 (d, J 2.2 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 20.15, 39.12, 40.52, 44.22, 48.87, 49.54, 124.16, 130.03, 138.34, 148.83, 150.90, 154.70. HRMS calcld for C₁₇H₂₅ClN₄O₂ 352.1666; found 352.1669. IR (KBr, cm⁻¹): 1726 and 1687 (C=O).

1-(2-(Methyl(phenyl)amino)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5k). Base: K₂CO₃. Reaction time: 2 h. The resulting solid was purified by column chromatography using a gradient of 80: 1 CH₂Cl₂: CH₃OH to afford yellow oil of 0.52 g (72%). mp 142~143 °C. ¹H NMR (500 MHz, CDCl₃): δ 3.07 (s, 3H), 3.37 (t, J 8.1 Hz, 2H), 3.82 (t, J 8.1 Hz, 2H), 4.46 (s, 2H), 4.74 (s, 2H), 6.70-6.73 (m, 3H), 7.21 (t, J 7.9 Hz, 2H), 7.37 (d, J 8.2 Hz, 1H), 7.65 (dd, J 2.4, 8.2 Hz, 1H), 8.34 (d, J 2.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 39.06, 39.42, 41.07, 44.60, 55.93, 112.13, 116.92, 124.61, 129.05, 130.29, 138.80, 149.09, 149.29, 151.38, 154.96, 170.46. HRMS calcld for C₁₈H₁₉ClN₄O₂ 358.1197; found 358.1196. IR (KBr, cm⁻¹): 1722 and 1691 (C=O).

1-(2-(Benzo[d]thiazol-2-ylthio)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5l). Base: K₂CO₃. Reaction time: 1 h. White solid: 0.75 g (90%). mp 158~159 °C. ¹H NMR (500 MHz, CDCl₃): δ 3.39 (t, J 8.1 Hz, 2H), 3.89 (t, J 8.1 Hz, 2H), 4.48 (s, 2H), 4.84 (s, 2H), 7.28-7.31 (m, 1H), 7.36 (d, J 8.2 Hz, 1H), 7.38-7.42 (m, 1H), 7.66 (dd, J 2.4, 8.2 Hz, 1H), 7.75 (d, J 7.8 Hz, 1H), 7.83 (d, J 8.0 Hz, 1H), 8.35 (d, J 2.4 Hz, 1H); ¹³C NMR (125 MHz, CDCl₃): δ 37.10, 39.64, 40.65, 44.62, 120.94, 121.63, 124.32, 124.66, 125.95, 130.14, 135.44, 138.83, 149.27, 151.44, 152.96, 154.49, 165.31, 167.22. HRMS calcld for C₁₈H₁₅ClN₄O₂S₂ 418.0325; found 418.0327. IR (KBr, cm⁻¹): 1726 and 1674 (C=O).
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References


