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 ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, high-resolution mass spectroscopy, IR and elemental analysis.

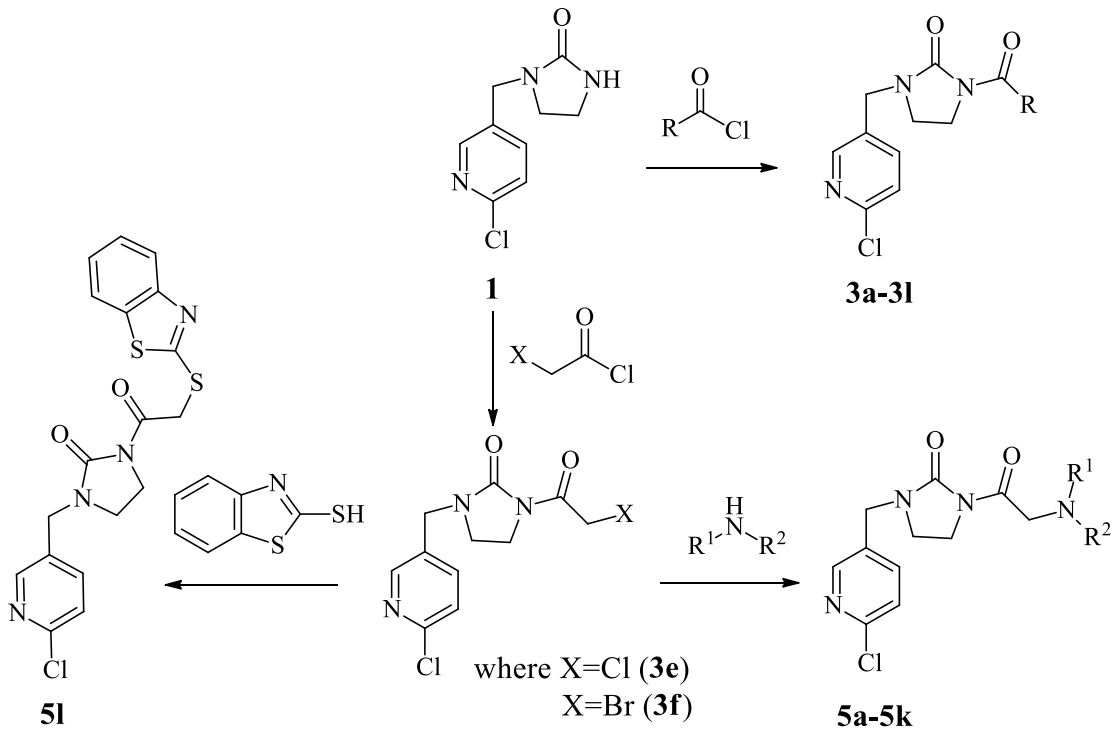
Keywords: Acylation, cyclic urea, *N*-heterocycles

Introduction

The cyclic urea derivatives have been reported to display a wide range of biological activities, such as the HIV protease inhibitors,[1] selective NK_1 antagonists,[2] Chk_1 inhibitors,[3] calcium-selective fluoroionophore,[4] anti-Alzheimer's disease[5] 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**),[22] 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

Entry	Solvent	Time/h	Base	Temperature/°C	Isolated yield/%
1	Toluene	22	not	70	30
2	Toluene	12	not	90	67
3	Toluene	9	not	110	73
4	Toluene	4	C_5H_5N	110	80
5	Toluene	1	Et_3N	110	89
6	THF	1	Et_3N	66	83
7	CH_2Cl_2	5	Et_3N	40	78

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 ºC to 110 ºC 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 (C_5H_5N), the yield of **3g** increased significantly to 80% in 4 h (entry 4). In contrast, in the presence of triethylamine (Et_3N), the yield of **3g** reached to 89% in 1 h (entry 5). Therefore, Et_3N is more effective for the reaction. Moreover, the effects of solvents such as toluene, THF and CH_2Cl_2 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**

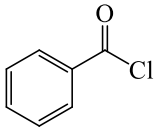
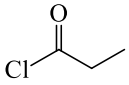
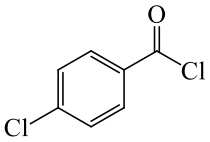
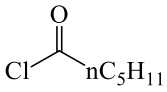
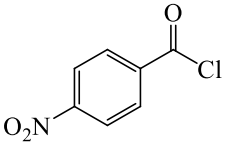
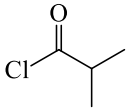
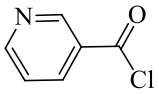
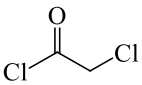
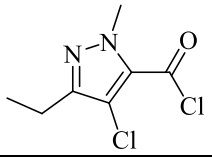
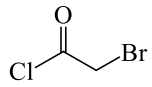
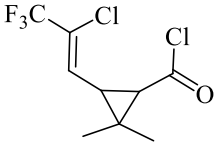
Entry	Acid chloride (**2a-2f**)	Product	Isolated yield/%	Entry	Acid chloride (**2g-2l**)	Product	Isolated yield/%
1		**3a**	93	7		**3g**	91
2		**3b**	84	8		**3h**	94
3		**3c**	89	9		**3i**[b]	53
4		**3d**	87	10		**3j**[c]	53
5		**3e**[a]	95	11		**3k**[c]	35

Table 2. Continued

Entry	Acid chloride (2a-2f)	**Product**	Isolated yield/%	Entry	Acid chloride (2g-2l)	**Product**	Isolated yield/%
6		**3f**[a]	89	12		**3l**[c]	58

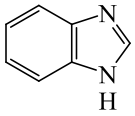
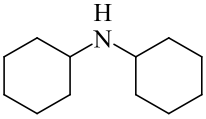
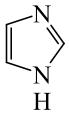
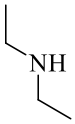
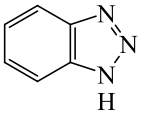
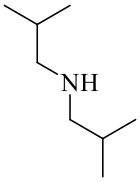
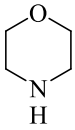
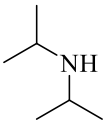
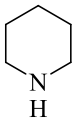
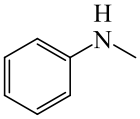
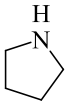
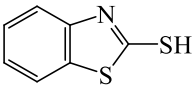
Reaction conditions: **1** (5 mmol), **2a-2l** (7.5 mmol), Et_3N (5 mmol), THF (10 mL), reflux.
[a] Without Et_3N, CH_2Cl_2 (10 mL), room temperature. [b] toluene (10 mL), reflux. [c] CH_2Cl_2 (10 mL), reflux.

In a further step, reactions of **1** with various acyl chlorides were carried out in the presence of Et_3N. 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 CH_2Cl_2 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 K_2CO_3 or $NaHCO_3$, nucleophilic substitution reactions of **3e** or **3f** and secondary amines were carried out in CH_3CN 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**

Entry	Amine (**4a-4f**)	Product	Isolated yield/%	Entry	Amine (**4g-4l**)	Product	Isolated yield/%
1		**5a**	71	7		**5g**[a,b]	49
2		**5b**	50	8		**5h**	69
3		**5c**	58	9		**5i**	86
4		**5d**	72	10		**5j**[a,b]	63
5		**5e**	78	11		**5k**	72
6		**5f**	61	12		**5l**[b]	90

Reaction conditions: **3e** (2 mmol), **4a-4l** (2-2.4 mmol), $NaHCO_3$ (2 mmol), CH_3CN (10 mL), 82 °C. [a] X = Br (**3f**). [b] K_2CO_3 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_3N (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_2Cl_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 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{11}H_{12}ClN_3O_2$ 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 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.17 (t, *J* 7.4 Hz, 3H), 2.96 (q, *J* 7.4 Hz, 2H), 3.33 (t, *J* 8.0 Hz, 2H), 3.84 (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, $CDCl_3$): δ 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 $C_{12}H_{14}ClN_3O_2$: 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 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{15}H_{20}ClN_3O_2$ 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 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{13}H_{16}ClN_3O_2$ 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 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{11}H_{11}Cl_2N_3O_2$: C 45.85, H 3.85, N 14.58%; found C 46.19, H 3.76, N 14.17%. IR (KBr, cm^{-1}): 1726 and 1691 (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 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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 (dd, *J* 2.4, 8.1 Hz, 1H), 8.33 (d, *J* 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{11}H_{11}ClBrN_3O_2$ 330.9723; found 330.9722. IR (KBr, cm^{-1}): 1726 and 1687 (C=O).

1-Benzoyl-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (3g). Reaction time: 1 h. White solid: 1.43 g (91%). mp 77~78 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 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 $C_{16}H_{14}ClN_3O_2$: 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 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 40.53, 44.61, 124.61, 127.82, 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 $C_{16}H_{13}Cl_2N_3O_2$: 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 ºC. ^{1}H NMR (500 MHz, $CDCl_3$): δ 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, $CDCl_3$): δ 40.27, 40.64, 44.70, 122.87, 124.72, 129.36, 130.01, 138.85, 140.22, 149.13, 149.32, 151.63,

153.82, 168.02. Anal. calcd for $C_{16}H_{13}ClN_4O_4$: C 53.27, H 3.63, N 15.53%; found C 53.42, H 3.97, N 15.53%. IR (KBr, cm^{-1}): 1728 and 1675 (C=O).

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 N_2. 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 CH_2Cl_2 (10 mL). A solution of **1** (0.42 g, 2 mmol) and dry Et_3N (0.20 g, 2 mmol) in dry CH_2Cl_2 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 $NaHCO_3$ and extracted with CH_2Cl_2 (3×15 mL). The organic layer were combined, washed with brine (20 mL) and dried over $MgSO_4$. 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 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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) ; ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{15}H_{13}ClN_4O_2$: 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-1*H*-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 N_2. 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 CH_2Cl_2 (10 mL). A solution of **1** (0.42 g, 2 mmol) and Et_3N (0.20 g, 2 mmol) in dry CH_2Cl_2 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 $NaHCO_3$ and extracted with DCM (3×15 mL). The organic layer were combined, washed with brine (20 mL) and dried over $MgSO_4$. 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 45~46 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 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), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.78, 19.19, 38.56, 40.27, 40.78, 44.58, 110.03, 124.72, 130.23, 132.98, 138.89, 149.27, 149.65, 151.54, 152.98, 159.16. HRMS calcd for $C_{16}H_{17}Cl_2N_5O_2$ 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 N_2 . 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 CH_2Cl_2 (10 mL) and placed under N_2. Subsequently, a solution of **1** (0.42 g, 2 mmol) and dry Et_3N (0.20 g, 2 mmol) in dry CH_2Cl_2 (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 $NaHCO_3$ was added and extracted with DCM (3×15 mL). The organic layer were combined, washed with brine (20 mL) and dried over $MgSO_4$. Solvent evaporation gave white solid of 0.49 g (58%). mp 131~132 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{18}H_{18}Cl_2N_3O_2F_3$ 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 $NaHCO_3$ (0.17 g, 2 mmol) or K_2CO_3 (0.14 g, 1 mmol) were dissolved in dry acetonitrile (CH_3CN) (10 mL) and stirred for 1 h at 82 ºC 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 ºC for 1-8 h (monitored by TLC). The solvent was evaporated at reduced pressure, then the residue was dissolved in CH_2Cl_2 (40 mL) and washed with H_2O and brine. The organic layer was dried over $MgSO_4$ and concentrated to afford the crude product, which was purified by column chromatography on SiO_2 eluting with appropriate solvents.

1-(2-(1*H*-benzo[*d*]imidazole-1-yl)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5a). Base: $NaHCO_3$. Reaction time: 2 h. The resulting solid was purified by column chromatography using a gradient of 40: 1 CH_2Cl_2: CH_3OH to yield white solid of 0.52 g (71%). mp 172~173 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): 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) ; ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{18}H_{16}ClN_5O_2$ 369.0993; found 369.0995. IR (KBr, cm^{-1}): 1726 and 1687 (C=O).

1-(2-(1*H*-imidazole-1-yl)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5b). Base: $NaHCO_3$. Reaction time: 3 h. White solid: 0.32 g (50%). mp 122~123 ºC. ^{1}H NMR (400 MHz, $CDCl_3$): 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) ; ^{13}C NMR (100 MHz, $CDCl_3$): 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 $C_{14}H_{14}ClN_5O_2$ 319.0836; found 319.0837. IR (KBr, cm^{-1}): 1722 and 1687 (C=O).

1-(2-(1*H*-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_2Cl_2: CH_3OH to yield white solid of 0.43 g (58%). mp 185~186 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 3.43 (t, *J* 7.6 Hz, 2H), 3.86 (t, *J* 7.6 Hz, 2H), 4.49 (s, 2H), 6.09 (s, 2H), 7.38 (d, *J* 7.7 Hz, 2H), 7.44-7.51 (m, 2H), 7.67 (d, *J* 7.7 Hz, 1H), 8.08 (d, *J* 8.2 Hz, 1H), 8.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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 $C_{17}H_{15}ClN_6O_2$ 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 ºC. ^1H NMR (400 MHz, $CDCl_3$): δ 2.65 (s, 4H), 3.37 (t, *J* 7.8 Hz, 2H), 3.78-3.87 (m, 8H), 4.43 (s, 2H), 7.36 (d, *J* 7.9 Hz, 1H), 7.63 (d, *J* 7.9 Hz, 1H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 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 $C_{15}H_{19}ClN_4O_3$ 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 ºC. ^1H NMR (500 MHz, $CDCl_3$): δ 1.42-1.47 (m, 2H), 1.62-1.66 (m, 4H), 2.57 (t, *J* 5.6 Hz, 4H), 3.35 (t, *J* 8.1 Hz, 2H), 3.79 (s, 2H), 3.84 (t, *J* 8.1 Hz , 2H), 4.42 (s, 2H), 7.35 (d, *J* 8.2 Hz, 1H), 7.63 (dd, *J* 2.4, 8.2 Hz, 1H), 8.32 (d, *J* 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{16}H_{21}ClN_4O_2$ 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 ºC. ^1H NMR (500 MHz, $CDCl_3$): δ 1.82-1.85 (m, 4H), 2.72 (t, *J* 6.6 Hz, 4H), 3.36 (t, *J* 8.1 Hz, 2H), 3.86 (t, *J* 8.1 Hz, 2H), 3.97 (s, 2H), 4.42 (s, 2H), 7.35 (d, *J* 8.2 Hz, 1H), 7.63 (dd, *J* 2.4, 8.2 Hz, 1H), 8.32 (d, *J* 2.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{15}H_{19}ClN_4O_2$ 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_2CO_3. Reaction time: 6.5 h. The resulting solid was purified by column chromatography using a gradient of 30: 1 CH_2Cl_2: CH_3OH to give yellow oil of 0.42 g (49%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.18-1.24 (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, 2H), 3.84 (t, *J* 7.6 Hz, 2H), 4.00 (s, 2H), 4.43 (s, 2H), 7.35 (d, *J* 8.0 Hz, 1H), 7.65 (d, *J* 8.0 Hz, 1H), 8.34 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 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 $C_{23}H_{33}ClN_4O_2$ 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: $NaHCO_3$. Reaction time: 1.5 h. Yellow oil: 0.45 g (69%). ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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 calcd for $C_{15}H_{21}ClN_4O_2$ 324.1353; found 324.1354. IR (KBr, cm^{-1}): 1722 and 1691 (C=O).

1-(2-(Diisobutylamino)acetyl)-3-((6-chloropyridin-3-yl)methyl)imidazolidin-2-one (5i). Base: $NaHCO_3$. Reaction time: 5.5 h. Yellow oil: 0.65 g (86%); ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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 calcd for $C_{19}H_{29}ClN_4O_2$ 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: K_2CO_3. Reaction time: 8 h. The resulting solid was purified by column chromatography using a gradient of 30: 1 CH_2Cl_2: CH_3OH to afford yellow oil of 0.44 g (63%). ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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 calcd for $C_{17}H_{25}ClN_4O_2$ 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: K_2CO_3. Reaction time: 2 h. The resulting solid was purified by column chromatography using a gradient of 80: 1 CH_2Cl_2: CH_3OH to afford yellow solid of 0.52 g (72%). mp 142~143 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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 calcd for $C_{18}H_{19}ClN_4O_2$ 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: K_2CO_3. Reaction time: 1 h. White solid: 0.75 g (90%). mp 158~159 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 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); ^{13}C NMR (125 MHz, $CDCl_3$): 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 calcd for $C_{18}H_{15}ClN_4O_2S_2$ 418.0325; found 418.0327. IR (KBr, cm^{-1}): 1726 and 1674 (C=O).

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