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ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 12303–12309

A facile and efficient method for the synthesis of novel pyridone analogues by aminolysis of an ester under solvent-free conditions

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Received 24 July 2007; revised 14 September 2007; accepted 27 September 2007
Available online 29 September 2007

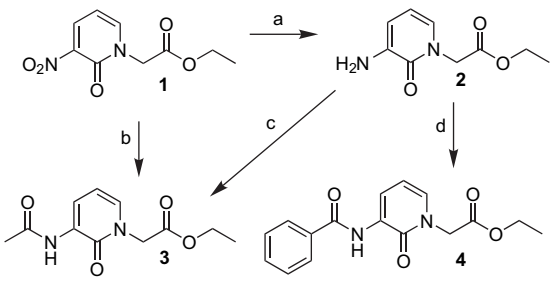
Abstract—A series of 15 pure novel *N*-alkylated pyridone derivatives have been synthesized in 73–96% yields on treatment of ethyl (2-pyridone)acetates with structurally diverse amines in an efficient aminolysis procedure under 'solvent-free' conditions.

1. Introduction

Pyridone based peptidomimetics have found utility as elastase,[1–6] caspase-1,[7,8] and non-transition state protease[9] and thrombin[10,11] inhibitors. Tethering peptide and non-peptide functionalities, primarily at the 1, 3, and 4 positions of the pyridone ring, has provided structural diversity leading to compounds with high selectivity against key enzymatic targets. Notably, extension of pyridone scaffolds to create amide linked moieties in the side chains relies almost exclusively on coupling of activated carboxylic acids (activated in situ) and amines. Although moderate to good yields can be obtained, this approach is time consuming, by being a multi-step process, and not atom-efficient. By comparison, approaches to simple amides from an amine and ester (without an attached pyridone ring) use either strongly basic[12–15] or metallic catalysts,[16–24] high pressure reactions[25] or microwave ester aminolysis,[26] or alternately, microwave reaction of an acid and primary amine.[27–30] Here we report on the development of a facile and atom-efficient protocol for the synthesis of *N*-alkyl amide side chains on a pyridone under 'solvent-free' conditions.

2. Results and discussion

The reactants for amide side-chain extension, esters **3** and **4**, were prepared as shown in Scheme 1, commencing with a modification of a literature preparation for aminopyridone **2**.[31,2] Commercially available 2-hydroxy-3-nitropyridine was treated with sodium hydride and ethyl bromoacetate to afford *N*-alkylated nitropyridone **1**. Treatment of **1** with hydrogen gas in the presence of 10% Pd/C in EtOAc afforded amine **2**, but required dilute reaction conditions on a larger scale (8–10 g). More concentrated reaction conditions for the conversion of nitropyridone **1** to amine **2** typically gave mixtures of starting nitropyridone **1**, amine **2**, and side products. Decomposition of amine **2** occurred rapidly within 24 h and therefore amine **2** was used directly in the next step. Acylation of amine **2** with acetyl chloride gave **3**, and with benzoyl chloride gave **4**. Next, treatment of nitropyridone **1** with hydrogen gas, 10% Pd/C, and acetic anhydride (1 equiv) in EtOAc directly gave acetylpyridone **3** in 99% yield and represents an efficient one-pot synthesis from pyridone **1**. The corresponding reaction with benzoic acid anhydride was not successful, the product being amine **2** with only minor amounts of benzoyl ester **4**. Heating this reaction did not change the result.



Scheme 1. Reagents and conditions: (a) 10% Pd/C, H_2, EtOAc, 16 h, 100%; (b) 10% Pd/C, H_2, acetic acid anhydride, EtOAc, rt, 16 h, 99%; (c) acetyl chloride, triethylamine, dry CH_2Cl_2, rt, 4 h, 98%; (d) benzoyl chloride, triethylamine, dry CH_2Cl_2, rt, 4 h, 99%.

Next, extension of the *N*-alkyl side chain on the pyridone ring using an atom-efficient procedure to form amide

Keywords: Aminolysis; Pyridone; Solvent-free.
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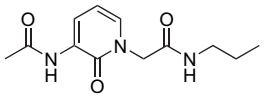
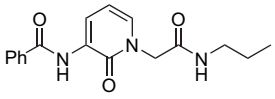
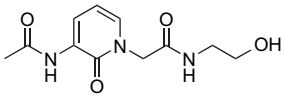
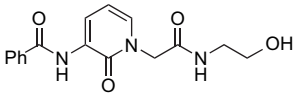
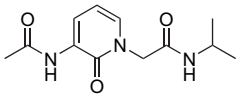
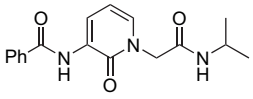
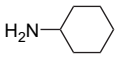
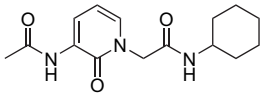
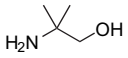
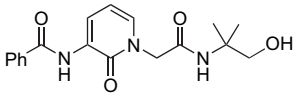
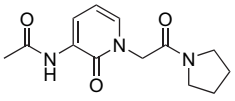
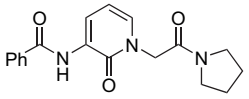
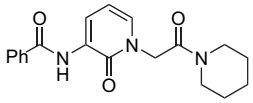
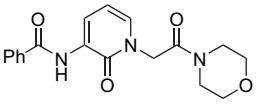
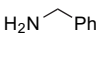
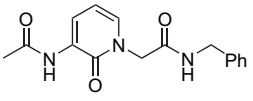
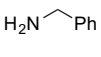
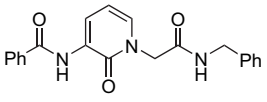
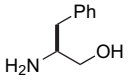
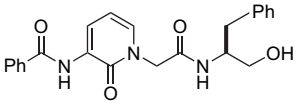
doi:10.1016/j.tet.2007.09.068

Table 1. Synthesis of pyridones **5**–**19** from aminolysis of pyridone esters **3** and **4**

Entry	Amine	Ester	Reaction conditions[a]	Product	Product structure	Isolated yield (%)
1	H_2N–$CH_2CH_2CH_3$	**3**	22 °C, 15 min	**5**		84
2	H_2N–$CH_2CH_2CH_3$	**4**	22 °C, 15 min	**6**		91
3	H_2N–CH_2CH_2OH	**3**	22 °C, 15 min	**7**		96
4	H_2N–CH_2CH_2OH	**4**	22 °C, 15 min	**8**		87
5	H_2N–$CH(CH_3)_2$	**3**	22 °C, 16 h	**9**		89
6	H_2N–$CH(CH_3)_2$	**4**	22 °C, 16 h	**10**		87
7		**3**	120 °C, 2 h	**11**		81
8		**4**	120 °C, 16 h	**12**		73
9		**3**	90 °C, 4 h	**13**		90
10		**4**	90 °C, 4 h	**14**		95
11		**4**	120 °C, 2 h	**15**		92[b]
12		**4**	120 °C, 48 h	**16**		86[b]
13		**3**	120 °C, 4 h	**17**		85
14		**4**	120 °C, 2 h	**18**		94
15		**4**	Melt, 120 °C, 1 h[c]	**19**		82

[a] Typically 5 μL of amine was used per mg of ester **3** or **4**; amine bp; entries 1 and 2, 48 °C; entries 3 and 4, 170 °C; entries 5 and 6, 33–34 °C; entry 7, 134 °C; entry 8, 134–136 °C; entries 9 and 10, 87–88 °C; entry 11, 106 °C; entry 12, 129 °C; entries 13 and 14, 184–185 °C; entry 15, mp, 91–92 °C.
[b] Purified by silica column chromatography.
[c] Mole ratio of amine to ester was 1:1.

analogues was explored. We initially attempted the aminolysis of pyridone ester **4** using a microwave reactor.[27] Aminolysis of benzoyl ester **4** with benzylamine at 120 °C, 200 W for 1 h gave a crude yield of pyridone **18** (99%), comparable to the crude yield (99%) obtained under thermal conditions (120 °C, 2 h), but with a lower crude purity.

However, with less reactive amines such as morpholine, the microwave method required much longer reaction times and/or higher reaction temperatures. For example, microwave aminolysis of benzoyl ester **4** with morpholine at 200 °C, 200 W for 80 min still gave incomplete conversion of the starting ester **4** and an increase in the side products was observed. This result highlighted the need for a controlled reaction temperature and suggested that direct aminolysis under controlled thermal conditions could provide a simple and clean reaction. Herein we report that direct aminolysis of pyridone esters **3** and **4**, in the absence of other solvents, using commercially available amines, gives facile access to the novel pyridone amides **5**–**19**, in excellent yields (73–96%) (Table 1) and purity (95–99%) without recourse to a microwave reactor.

Thus, pyridone ester (**3** or **4**, 100 mg) was heated with excess of the amine (0.5 mL), at a reaction temperature of 22, 90, or 120 °C, and with a reaction time between 15 min and 48 h depending on the boiling point and reactivity of the amine (Table 1). Facile isolation of the product was through the removal of excess amine under vacuum, or by diluting the crude reaction mixture with ether, whereupon the product crashed out as a solid.

The aminolysis proceeded readily with primary amines when the amino group was attached to a 1°, 2°, or 3° carbon atom (entries 1–8 and 13–15, Table 1), and with some common secondary amines (entries 9–12, Table 1). A melt procedure was required for the reaction of a solid amine (mp 91–92 °C) (entry 15, Table 1). Other amines such as diethylamine and aniline were unreactive, under the general reaction conditions. Modifying the reaction conditions with these amines, such as inclusion of a polar solvent (e.g., water, ethanol), addition of a Lewis acid ($MgCl_2$, $ZnCl_2$, or $CeCl_3$), or use of microwave conditions, did not produce the desired products. Poor reactivity was attributed to reduced nucleophilicity, such as in the aromatic amine aniline, and a combination of steric factors, and/or a low boiling point, in the case of diethylamine (the boiling point of diethylamine is only 55 °C, cf. pyrrolidine, 88 °C). By comparision, piperidine (entry 11, Table 1) was relatively reactive due to the increased nucleophilic nitrogen atom (cf. diethylamine), and in morpholine, the β-oxygen atom either inductively or otherwise reduces the nucleophilicity of the nitrogen, thus requiring more forcing reaction conditions (entry 12, Table 1).

3. Conclusions

The direct aminolysis of pyridone esters **3** and **4** with a range of primary amines and heterocyclic secondary amines is a very simple procedure that produces the corresponding novel pyridone amides in high yield and purity. Direct aminolysis is an effective process with the potential for easy scale-up. It avoids multi-step peptide coupling procedures, chromatography to remove by-products, and the need for technical instrumentation (such as a microwave reactor). It represents a mild and efficient process for *N*-alkyl side-chain extension of pyridones and should be of interest for other applications in organic synthesis.

4. Experimental

4.1. General procedures

See Supplementary data.

4.2. General method

4.2.1. Method A (aminolysis at 90 or 120 °C). Aminolysis was carried out in a conical micro-scale reaction vessel by mixing amine (5 μL amine per mg of ester **4** or **5**) with ester (**4** or **5**) (0.1–1.0 g). The reaction mixture was heated for 2, 4, or 16 h at 90 or 120 °C (see Table 1), then transferred while still warm to a conical flask, and diluted with diethyl ether. The diethyl ether mixture was cooled in a freezer overnight (16 h) and the excess amine was separated from the crude solid product by filtration and washing with additional diethyl ether. The crude solid was recrystallized by dissolving in hot acetone and then adding small amounts of diethyl ether, the resulting solution was cooled in a freezer overnight forming a white solid. The white solid was filtered and washed with diethyl ether giving the desired amides in >70% yields and in 95–99% purity, as determined by ^{1}H NMR spectroscopy. Esters **15** and **16** were further purified by silica column chromatography (EtOAc/CH_2Cl_2 with 0.5% Et_3N).

4.2.2. Method B (aminolysis at room temperature). Aminolysis was carried out according to method A with the reaction mixture stirred at room temperature for 15 min or 16 h. The reaction mixture was worked up as for method A.

4.2.3. Method C (aminolysis with solid melt). A 1:1 equimolar mixture of ester **4** and solid amine was melted together and transferred to a conical micro-scale reaction vessel. The resulting solid mixture was placed in a pre-heated oil bath at 120 °C. Heating was carried out without stirring until a solution was formed and then with stirring until all eliminated ethanol was evaporated and a solid formed, or for 4 h if no solid was formed. The crude reaction mixture was transferred to a conical flask and re-dissolved in warm acetone. Small amounts of diethyl ether were added and the resulting solution cooled in a freezer overnight forming a white solid. The white solid was filtered and washed with diethyl ether giving the desired amide in >80% yield and in 99% purity, as determined by ^{1}H NMR spectroscopy.

4.2.3.1. 2′-[3-(Acetylamino)-2-oxopyridin-1(2*H*)-yl]-*N*-propylacetamide (5). Ester **3** (0.35 g, 1.47 mmol) and propylamine (1.8 mL) were treated at room temperature for 15 min using method B. Compound **5** was obtained as a colorless solid (0.31 g, 84.0%): mp 170–172 °C (dec); IR (KBr) ν 3289, 1663, 1646, 1601, 760, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.84 (t, 3H, J=7.2 Hz, CH_3), 1.46 (tq, 2H, J=7.2, 7.2 Hz, CH_2–CH_3), 2.15 (s, 3H, CH_3–CO), 3.14 (dt, 2H, J=6.8, 6.0 Hz, NH–CH_2), 4.56 (s, 2H, H2′), 6.26 (dd, 1H, J=7.2, 7.2 Hz, H5), 6.83 (br s, 1H, $W_{1/2}$~14 Hz, NH–CH_2), 7.06 (dd, 1H, J=7.2, 1.6 Hz, H6), 8.35 (m, 2H, H4, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 11.5 (CH_3), 22.8 (CH_2–CH_3), 24.8 (CH_3–CO), 41.6 (NH–CH_2), 53.8 (C2′), 107.6 (C5), 123.2 (C4), 129.5 (C3), 130.9 (C6), 157.6 (C2), 166.7 (C1′), 169.4 (CO); LRMS (ESI) m/z (%): 274.2 ([M+Na]$^+$, 100), 258.2 ([M+Li]$^+$,

100); HRMS: calcd for $[M+Na]^+$ $C_{12}H_{17}O_3N_3 \cdot Na$ 274.1162, found 274.1162.

4.2.3.2. *N*-{1-[2′-(Propylamino)-2′-oxoethyl]-2-oxo-1,2-dihydropyridin-3-yl}benzamide (6). Ester **4** (0.95 g, 3.16 mmol) and propylamine (4.8 mL) were treated at room temperature for 15 min using method B. Compound **6** was obtained as a colorless solid (0.90 g, 91%): mp 214–215 °C; IR (KBr) ν 3289, 1654, 1527 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 0.85 (t, 3H, J=7.2 Hz, CH_3), 1.42 (tq, 2H, J=7.2, 7.0 Hz, CH_2–CH_3), 3.04 (dt, 2H, J=6.8, 5.6 Hz, NH–CH_2), 4.62 (s, 2H, H1′), 6.33 (dd, 1H, J=6.8, 6.8 Hz, H5), 7.40 (dd, 1H, J=6.8, 1.6 Hz, H6), 7.52–7.55 (m, 2H, *m*-Ph), 7.59–7.63 (m, 1H, *p*-Ph), 7.89–7.92 (m, 2H, *o*-Ph), 8.19 (br t, 1H, J=5.6 Hz, NH–CH_2), 8.28 (dd, 1H, J=7.2, 1.6 Hz, H4), 9.28 (br s, 1H, $W_{1/2}$~8 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 11.4 (CH_3), 22.3 (CH_2–CH_3), 40.5 (NH–CH_2), 51.6 (C1′), 104.8 (C5), 123.6 (C4), 127.1 (*o*-Ph), 128.0 (C3), 128.8 (*m*-Ph), 132.0 (*p*-Ph), 133.7 (*i*-Ph), 133.9 (C6), 157.1 (C2), 164.8 (CO), 166.2 (C2′); LRMS (ESI) *m*/*z* (%): 336.2 ($[M+Na]^+$, 100), 314.2 ($[M+H]^+$, 40), 320.3 ($[M+Li]^+$, 100). Anal. Calcd for $C_{17}H_{19}O_3N_3$: C, 65.16; H, 6.11; N, 13.41%. Found: C, 65.16; H, 5.96; N, 13.28%.

4.2.3.3. 2-[3′-(Acetylamino)-2′-oxopyridin-1′(2*H*)-yl]-*N*-(2″-hydroxyethyl)acetamide (7). Ester **3** (0.10 g, 0.42 mmol) and ethanolamine (0.5 mL) were treated at room temperature for 15 min using method B. Compound **7** was obtained as a colorless solid (0.102 g, 96%): mp 212–214 °C (dec); IR (KBr) ν 3293, 1650, 1609, 1528, 756 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.09 (s, 3H, CH_3), 3.14 (dt, 2H, J=6.0, 6.0 Hz, H1″), 3.40 (dt, 2H, J=6.0, 5.6 Hz, H2″), 4.57 (s, 2H, H2), 4.67 (t, 1H, J=5.6 Hz, OH), 6.21 (dd, 1H, J=7.2, 7.2 Hz, H5), 7.28 (dd, 1H, J=6.8, 1.6 Hz, H6), 8.16–8.20 (m, 2H, NH–CH_2, H4), 9.19 (br s, 1H, $W_{1/2}$~5 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 24.7 (CH_3), 42.3 (C1″), 52.3 (C2), 60.4 (C2″), 105.3 (C5), 123.4 (C4), 129.3 (C3), 133.5 (C6), 157.4 (C2), 167.3 (C1), 169.9 (CO); LRMS (ESI) *m*/*z* (%): 276.1 ($[M+Na]^+$, 100), 254.1 ($[M+H]^+$, 20), 260.1 ($[M+Li]^+$, 100). Anal. Calcd for $C_{11}H_{15}O_4N_3$: C, 52.17; H, 5.97; N, 16.59%. Found: C, 51.93; H, 5.98; N, 16.36%.

4.2.3.4. *N*-(1-{2′-[(2″-Hydroxyethyl)amino]-2′-oxoethyl}-2-oxo-1,2-dihydropyridin-3-yl)benzamide (8). Ester **4** (0.40 g, 1.33 mmol) and ethanolamine (2.0 mL) were treated at room temperature for 15 min using method B. Compound **8** was obtained as a colorless solid (0.37 g, 87%): mp 213–216 °C (dec); IR (KBr) ν 3420, 3301, 1650, 1516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.15 (dt, 2H, J=6.0, 5.6 Hz, H1″), 3.42 (dt, 2H, J=6.0, 5.6 Hz, H2″), 4.64 (s, 2H, H1′), 4.69 (t, 1H, J=5.6 Hz, OH), 6.33 (dd, 1H, J=7.0, 7.0 Hz, H5), 7.39 (dd, 1H, J=6.4, 1.6 Hz, H6), 7.52–7.56 (m, 2H, *m*-Ph), 7.59–7.63 (m, 1H, *p*-Ph), 7.89–7.91 (m, 2H, *o*-Ph), 8.24 (br t, 1H, J=5.4 Hz, NH–CH_2), 8.28 (dd, 1H, J=8.0, 1.6 Hz, H4), 9.28 (br s, 1H, $W_{1/2}$~5 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 41.6 (C1″), 51.5 (C1′), 59.7 (C2″), 104.9 (C5), 123.6 (C4), 127.1 (*o*-Ph), 128.0 (C3), 128.8 (*m*-Ph), 132.0 (*p*-Ph), 133.7 (C6), 133.9 (*i*-Ph), 157.1 (C2), 164.8 (CO), 166.4 (C2′); LRMS (ESI) *m*/*z* (%): 338.3 ($[M+Na]^+$, 100), 316.3 ($[M+H]^+$, 10), 322.3 ($[M+Li]^+$, 100). Anal. Calcd for $C_{16}H_{17}O_4N_3$: C, 60.94; H, 5.43; N, 13.33%. Found: C, 60.66; H, 5.41; N, 13.10%.

4.2.3.5. 2′-[3-(Acetylamino)-2-oxopyridin-1(2*H*)-yl]-*N*-isopropylacetamide (9). Ester **3** (0.30 g, 1.26 mmol) and isopropylamine (1.5 mL) were treated at room temperature for 16 h using method B. Compound **9** was obtained as a colorless solid (0.28 g, 89%): mp 119–121 °C (dec); IR (KBr) ν 3342, 3265, 1695, 1655, 1597, 1540, 1516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.06 (d, 6H, J=6.4 Hz, CH–CH_3), 2.09 (s, 3H, CH_3), 3.81 (dsept (eight lines), 1H, J=7.2, 7.0 Hz, CH), 4.52 (s, 2H, H1′), 6.20 (dd, 1H, J=7.2, 7.2 Hz, H5), 7.28 (dd, 1H, J=7.2, 1.6 Hz, H6), 8.07 (br d, 1H, J=7.6 Hz, NH–CH), 8.17 (dd, 1H, J=7.2, 1.6 Hz, H4), 9.20 (br s, 1H, $W_{1/2}$~8 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.4 (CH–CH_3), 24.0 (CH_3), 40.7 (CH), 51.6 (C1′), 104.5 (C5), 122.8 (C4), 128.6 (C3), 133.0 (C6), 156.7 (C2), 165.4 (C2′), 169.2 (CO); LRMS (ESI) *m*/*z* (%): 274.2 ($[M+Na]^+$, 100), 258.2 ($[M+Li]^+$, 100). Anal. Calcd for $C_{12}H_{17}O_3N_3$: C, 57.36; H, 6.82; N, 16.72%. Found: C, 57.21; H, 6.95; N, 16.54%.

4.2.3.6. *N*-{1-[2′-(Isopropylamino)-2′-oxoethyl]-2-oxo-1,2-dihydropyridin-3-yl}benzamide (10). Ester **4** (0.35 g, 1.17 mmol) and isopropylamine (1.75 mL) were treated at room temperature for 16 h using method B. Compound **10** was obtained as a colorless solid (0.32 g, 87%): mp 212–215 °C (dec); IR (KBr) ν 3375, 3285, 1650, 1520, 760 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.07 (d, 6H, J=6.8 Hz, CH_3), 3.83 (dsept (eight lines), 1H, J=6.8, 6.6 Hz, CH), 4.59 (s, 2H, H1′), 6.32 (dd, 1H, J=7.2, 7.2 Hz, H5), 7.39 (dd, 1H, J=7.2, 1.6 Hz, H6), 7.52–7.55 (m, 2H, *m*-Ph), 7.59–7.62 (m, 1H, *p*-Ph), 7.89–7.91 (m, 2H, *o*-Ph), 8.11 (br d, 1H, J=8.0 Hz, NH–CH), 8.27 (dd, 1H, J=7.2, 1.6 Hz, H4), 9.28 (br s, 1H, $W_{1/2}$~5 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 22.4 (CH_3), 40.7 (CH), 51.5 (C1′), 104.7 (C5), 123.7 (C4), 127.1 (*o*-Ph), 128.0 (*m*-Ph), 128.8 (C3), 132.0 (*p*-Ph), 133.8 (C6), 133.9 (*i*-Ph), 157.1 (C2), 164.8 (CO), 165.3 (C2′); LRMS (ESI) *m*/*z* (%): 336.3 ($[M+Na]^+$, 100), 314.3 ($[M+H]^+$, 10), 320.3 ($[M+Li]^+$, 100). Anal. Calcd for $C_{17}H_{19}O_3N_3$: C, 65.16; H, 6.11; N, 13.41%. Found: C, 65.11; H, 6.03; N, 13.19%.

4.2.3.7. 2′-[3-(Acetylamino)-2-oxopyridin-1(2*H*)-yl]-*N*-cyclohexylacetamide (11). Ester **3** (0.10 g, 0.42 mmol) and cyclohexylamine (0.5 mL) were treated at 120 °C for 4 h using method A. Compound **11** was obtained as a colorless solid (0.099 g, 81%): mp 229–230 °C (dec); IR (KBr) ν 3500, 3297, 1645 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.11–1.29 (m, 5H, $(CH_2)_5$), 1.57–1.55 (m, 1H, $(CH_2)_5$), 1.65–1.74 (m, 4H, $(CH_2)_5$), 2.09 (s, 3H, CH_3), 3.46–3.57 (m, 1H, CH), 4.54 (s, 2H, H1′), 6.20 (dd, 1H, J=7.2, 7.2 Hz, H5), 7.28 (dd, 1H, J=7.2, 1.8 Hz, H6), 8.07 (br d, 1H, J=8.0 Hz, NH–CH), 8.17 (dd, 1H, J=7.2, 1.8 Hz, H4), 9.20 (br s, 1H, $W_{1/2}$~5 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.9 (CH_3), 24.4 ($(CH_2)_5$), 25.2 ($(CH_2)_5$), 32.4 ($(CH_2)_5$), 47.7 (CH), 51.6 (C1′), 104.5 (C5), 122.7 (C4), 128.6 (C3), 132.9 (C6), 156.7 (C2), 165.4 (C2′), 169.2 (CO); LRMS (ESI) *m*/*z* (%): 314.3 ($[M+Na]^+$, 100), 292.3 ($[M+H]^+$, 15), 298.3 ($[M+Li]^+$, 100); HRMS: calcd for $[M+Na]^+$ $C_{15}H_{21}O_3N_3 \cdot Na$ 314.1475, found 314.1460.

4.2.3.8. *N*-(1-{2′-[(2″-Hydroxy-1″,1″-dimethylethyl)-amino]-2′-oxoethyl}-2-oxo-1,2-dihydropyridin-3-yl)benzamide (12). Ester **4** (0.20 g, 0.67 mmol) and 2-amino-2-methyl-1-propanol (1.0 mL) were treated at 120 °C for 4 h using method A. Compound **12** was obtained as a colorless solid (0.17 g, 73%): mp 185–187 °C; IR (KBr) ν 3457, 3301, 1671, 1642, 1597, 1528, 756, 707 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.19 (s, 6H, CH_3), 3.38 (d, 2H, J=5.6 Hz, H2″), 4.60 (s, 2H, H1′), 4.74 (t, 1H, J=5.6 Hz, OH), 6.32 (dd, 1H, J=7.0, 7.0 Hz, H5), 7.36 (dd, 1H, J=7.0, 1.8 Hz, H6), 7.52–7.56 (m, 2H, *m*-Ph), 7.59–7.63 (m, 1H, *p*-Ph), 7.72 (br s, 1H, $W_{1/2}$∼6 Hz, 2′-NH), 7.89–7.91 (m, 2H, *o*-Ph), 8.27 (dd, 1H, J=7.4, 1.8 Hz, H4), 9.28 (br s, 1H, $W_{1/2}$∼6 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.6 (CH_3), 51.7 (C1′), 54.6 (C1″), 67.1 (C2″), 104.7 (C5), 123.7 (C4), 127.1 (*o*-Ph), 127.9 (C3), 128.8 (*m*-Ph), 132.0 (*p*-Ph), 133.8 (*i*-Ph), 133.9 (C6), 157.1 (C2), 164.8 (CO), 165.8 (C2′); LRMS (ESI) *m*/*z* (%): 366.3 ($[M+Na]^+$, 100), 344.3 ($[M+H]^+$, 10), 350.3 ($[M+Li]^+$, 100). Anal. Calcd for $C_{18}H_{21}O_4N_3$: C, 62.96; H, 6.16; N, 12.24%. Found: C, 62.78; H, 6.30; N, 12.13%.

4.2.3.9. *N*-{2-Oxo-1-[2′-oxo-2′-(pyrrolidin-1″-yl)-ethyl]-1,2-dihydropyridin-3-yl}acetamide (13). Ester **3** (0.82 g, 3.45 mmol) and pyrrolidine (4.1 mL) were treated at 90 °C for 4 h using method A. Compound **13** was obtained as a colorless solid (0.82 g, 90%): mp 204–205 °C (dec); IR (KBr) ν 3450, 3297, 1667, 1589, 1503 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 1.84 (tt, 2H, J=6.8, 6.8 Hz, H3″ or H4″), 1.98 (tt, 2H, J=6.8, 6.8 Hz, H3″ or H4″), 2.12 (s, 3H, CH_3), 3.45 (t, 2H, J=7.0 Hz, H2″ or H5″), 3.54 (t, 2H, J=6.8 Hz, H2″ or H5″), 4.64 (s, 2H, H1′), 6.22 (t, 1H, J=7.2, 7.2 Hz, H5), 6.99 (dd, 1H, J=7.0, 1.8 Hz, H6), 8.33 (m, 2H, H4, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.2 (C3″ or C4″), 24.7 (CH_3), 26.2 (C3″ or C4″), 46.1 (C2″ or C5″), 46.3 (C2″ or C5″), 51.2 (C1′), 106.7 (C5), 122.7 (C4), 129.2 (C3), 131.2 (C6), 157.4 (C2), 164.4 (C2′), 169.1 (CO); LRMS (ESI) *m*/*z* (%): 286.2 ($[M+Na]^+$, 90), 264.2 ($[M+H]^+$, 100), 270.2 ($[M+Li]^+$, 100). Anal. Calcd for $C_{13}H_{17}O_3N_3$: C, 59.30; H, 6.51; N, 15.96%. Found: C, 59.26; H, 6.24; N, 15.74%.

4.2.3.10. *N*-{2-Oxo-1-[2′-oxo-2′-(pyrrolidin-1″-yl)-ethyl]-1,2-dihydropyridin-3-yl}benzamide (14). Ester **4** (0.87 g, 2.90 mmol) and pyrrolidine (4.4 mL) were treated at 90 °C for 4 h using method A. Compound **14** was obtained as a colorless solid (0.89 g, 94%): mp 169–172 °C (dec); IR (KBr) ν 3370, 1659, 1528, 772, 702 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.79 (tt, 2H, J=6.8, 6.8 Hz, H3″ or H4″), 1.93 (tt, 2H, J=6.8, 6.8 Hz, H3″ or H4″), 3.31 (t, 2H, J=6.8 Hz, H2″ or H5″), 3.52 (t, 2H, J=7.0 Hz, H2″ or H5″), 4.79 (s, 2H, H1′), 6.34 (dd, 1H, J=7.2, 7.2 Hz, H5), 7.37 (dd, 1H, J=6.8, 1.6 Hz, H6), 7.52–7.56 (m, 2H, *m*-Ph), 7.59–7.63 (m, 1H, *p*-Ph), 7.89–7.92 (m, 2H, *o*-Ph), 8.29 (dd, 1H, J=6.8, 1.6 Hz, H4), 9.28 (br s, 1H, $W_{1/2}$∼4 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.7 (C3″ or C4″), 25.6 (C3″ or C4″), 45.2 (C2″ or C5″), 45.7 (C2″ or C5″), 50.9 (C1′), 104.9 (C5), 123.6 (C4), 127.1 (*o*-Ph), 128.0 (C3), 128.8 (*m*-Ph), 132.1 (*p*-Ph), 133.5 (C6), 133.9 (*i*-Ph), 157.0 (C2), 164.3 (C2′), 164.8 (CO); LRMS (ESI) *m*/*z* (%): 348.2 ($[M+Na]^+$, 45), 326.2 ($[M+H]^+$, 100), 332.2 ($[M+Li]^+$, 100). Anal. Calcd for $C_{18}H_{19}O_3N_3$: C, 66.45; H, 5.89; N, 12.9%. Found: C, 66.46; H, 5.92; N, 12.93%.

4.2.3.11. *N*-{2-Oxo-1-[2′-oxo-2′-(piperidin-1″-yl)-ethyl]-1,2-dihydropyridin-3-yl}benzamide (15). Ester **4** (0.150 g, 0.499 mmol) and cyclohexylamine (0.75 mL) were treated at 120 °C for 2 h using method A. Compound **15** was obtained as a colorless solid (0.156 g, 92%): mp 166–167.5 °C (dec); IR (KBr) ν 3436, 3350, 1646, 1605, 1519 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 1.40–1.49 (m, 2H, H4″), 1.52–1.63 (m, 4H, H3″ and H5″), 3.40–3.50 (m, 5H, H2″ and H6″), 4.90 (s, 2H, H1′), 6.33 (dd, 1H, J=7.2, 7.2 Hz, H5), 7.36 (dd, 1H, J=7.2, 1.6 Hz, H6), 7.52–7.56 (m, 2H, *m*-Ph), 7.59–7.63 (m, 1H, *p*-Ph), 7.89–7.91 (m, 2H, *o*-Ph), 8.28 (dd, 1H, J=7.2, 1.6 Hz, H4), 9.28 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 23.9 (C3″ or C5″), 25.2 (C4″), 25.9 (C3″ or C5″), 42.5 (C2″ or C6″), 45.2 (C2″ or C6″), 50.2 (C1′), 104.8 (C5), 123.5 (C4), 127.1 (*o*-Ph), 128.0 (C3), 128.8 (*m*-Ph), 132.1 (*p*-Ph), 133.6 (C6), 133.9 (*i*-Ph), 157.1 (C2), 164.3 (C2′), 164.8 (CO); LRMS (ESI) *m*/*z* (%): 362.1 ($[M+Na]^+$, 100), 346.2 ($[M+Li]^+$, 100); HRMS: calcd for $[M+Na]^+$ $C_{19}H_{21}O_3N_3{\cdot}Na$ 362.1475, found 362.1488.

4.2.3.12. *N*-{1-[2-(Morpholin-4″-yl)-2′-oxoethyl]-2-oxo-1,2-dihydropyridin-3-yl}benzamide (16). Ester **4** (0.30 g, 1.00 mmol) and morpholine (1.5 mL) were treated at 120 °C for 48 h using method A. Compound **16** was obtained as a colorless solid (0.29 g, 86%): mp 157–160 °C; IR (KBr) ν 3359, 3085, 2856, 1646, 1597, 1516 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 3.43–3.45 (m, 2H, H2″ or H6″), 3.55–3.59 (m, 4H, H2″ or H6″, H3″ or H5″), 3.64–3.66 (m, 2H, H3″ or H5″), 4.92 (s, 2H, H1′), 6.34 (dd, 1H, J=6.8, 6.8 Hz, H5), 7.36 (dd, 1H, J=6.8, 1.6 Hz, H6), 7.52–7.56 (m, 2H, *m*-Ph), 7.59–7.64 (m, 1H, *p*-Ph), 7.89–7.92 (m, 2H, *o*-Ph), 8.29 (dd, 1H, J=7.0, 1.6 Hz, H4), 9.28 (br s, 1H, $W_{1/2}$∼5 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 41.9 (C2″ or C6″), 44.8 (C2″ or C6″), 50.1 (C1′), 66.0 (C3″ and C5″), 105.0 (C5), 123.6 (C4), 127.1 (*o*-Ph), 128.0 (C3), 128.8 (*m*-Ph), 132.1 (*p*-Ph), 133.5 (C6), 133.9 (*i*-Ph), 157.1 (C2), 164.8 (CO), 165.0 (C2′); LRMS (ESI) *m*/*z* (%): 364.3 ($[M+Na]^+$, 100), 342.3 ($[M+H]^+$, 10), 348.3 ($[M+Li]^+$, 100). Anal. Calcd for $C_{18}H_{19}O_4N_3$: C, 63.33; H, 5.61; N, 12.31%. Found: C, 63.26; H, 5.57; N, 12.15%.

4.2.3.13. 2′-[3-(Acetylamino)-2-oxopyridin-1(2*H*)-yl]-*N*-benzylacetamide (17). Ester **3** (0.20 g, 0.84 mmol) and benzylamine (1.0 mL) were treated at 120 °C for 4 h using method A. Compound **17** was obtained as a colorless solid (0.21 g, 84%): mp 203–205 °C (dec); IR (KBr) ν 3318, 3273, 1659, 1600, 1518, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 2.11 (s, 3H, CH_3), 4.31 (d, 2H, J=6.0 Hz, CH_2), 4.66 (s, 2H, H2′), 6.23 (t, 1H, J=7.2, 7.2 Hz, H5), 7.23–7.35 (m, 6H, Ph, H6), 8.21 (dd, 1H, J=7.2, 1.6 Hz, H4), 8.69 (br t, 1H, J=6.0 Hz, NH–CH_2), 9.24 (br s, 1H, $W_{1/2}$∼6 Hz, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.7 (CH_3), 42.9 (CH_2), 52.4 (C2′), 105.4 (C5), 123.5 (C4), 127.5 (*p*-Ph), 127.9 (*o*-Ph), 129.0 (*m*-Ph), 129.4 (C3), 133.6 (C6), 139.8 (*i*-Ph), 157.5 (C2), 167.3 (C1′), 170.0 (CO); LRMS (ESI) *m*/*z* (%): 322.1 ($[M+Na]^+$, 100), 306.2 ($[M+Li]^+$, 100). Anal. Calcd for $C_{16}H_{17}O_3N_3$: C, 64.20; H, 5.72; N, 14.04%. Found: C, 64.23; H, 5.75; N, 13.89%.

4.2.3.14. *N*-{1-[2′-(Benzylamino)-2′-oxoethyl]-2-oxo-1,2-dihydropyridin-3-yl}benzamide (18). Ester **4** (0.73 g, 2.43 mmol) and benzylamine (3.7 mL) were treated at

120 °C for 4 h using method A. Compound **18** was obtained as a colorless solid (0.82 g, 93%): mp 213–215 °C (dec); IR (KBr) ν 3285, 1650, 1524, 760, 698 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 4.31 (d, 2H, J=5.6 Hz, CH_2), 4.71 (s, 2H, H1′), 6.34 (dd, 1H, J=7.0, 7.0 Hz, H5), 7.22–7.35 (m, 5H, CH_2Ph), 7.44 (dd, 1H, J=7.0, 2.0 Hz, H6), 7.52–7.56 (m, 2H, *m*-Ph), 7.59–7.63 (m, 1H, *p*-Ph), 7.89–7.92 (m, 2H, *o*-Ph), 8.29 (dd, 1H, J=7.6, 2.0 Hz, H4), 8.72 (br t, 1H, J=6.0 Hz, NH–CH_2), 9.30 (br s, 1H, $W_{1/2}$~4 Hz, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 42.2 (NH–CH_2), 51.7 (C1′), 104.9 (C5), 123.7 (C4), 126.9 (*o*-Ph), 127.1 (CH_2Ph), 127.3 (CH_2Ph), 128.0 (C3), 128.3 (CH_2Ph), 128.8 (*m*-Ph), 132.1 (*p*-Ph), 133.7 (C6), 133.9 (*i*-Ph), 139.0 (*i*-CH_2Ph), 157.2 (C2), 164.9 (NH), 166.5 (C2′); LRMS (ESI) *m*/*z* (%): 384.2 ([M+Na]$^+$, 40), 362.2 ([M+H]$^+$, 100), 368.3 ([M+Li]$^+$, 100). Anal. Calcd for $C_{21}H_{19}O_3N_3$: C, 69.79; H, 5.30; N, 11.63%. Found: C, 69.83; H, 5.26; N, 11.63%.

4.2.3.15. *N*-(1-{2′-[(1″-Benzyl-2″-hydroxyethyl)amino]-2′-oxoethyl}-2-oxo-1,2-dihydropyridin-3-yl)benzamide (19). Ester **4** (0.30 g, 1.00 mmol) and (*S*)-2-amino-3-phenyl-1-propanol (0.15 g) were treated at 120 °C for 1 h using method C. Compound **19** was obtained as a colorless solid (0.33 g, 82%): mp 198–200 °C; IR (KBr) ν 3383, 3285, 1679, 1646, 1581, 1524, 702 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ 2.66 (dd, 1H, J=13.6, 7.6 Hz, CH_2Ph), 2.84 (dd, 1H, J=13.6, 7.6 Hz, CH_2Ph), 3.27–3.40 (m, 2H, H2″), 3.84–3.92 (m, 1H, H1″), 4.61 (ABq, 2H, J=15.6 Hz, H1′), 4.80 (t, 1H, J=5.4 Hz, H2″), 6.31 (dd, 1H, J=7.2, 7.2 Hz, H5), 7.15–7.31 (m, 6H, H6, CH_2Ph), 7.52–7.56 (m, 2H, *m*-Ph), 7.59–7.63 (m, 1H, *p*-Ph), 7.89–7.91 (m, 2H, *o*-Ph), 8.17 (d, 1H, J=8.0 Hz, NH–CH), 8.27 (dd, 1H, J=7.2, 1.6 Hz, H4), 9.28 (s, 1H, NH); ^{13}C NMR (100 MHz, DMSO-d_6): δ 37.2 (CH_2Ph), 52.1 (C1′), 53.6 (C1″), 62.8 (C2″), 105.5 (C5), 124.3 (C4), 126.7 (*p*-CH_2Ph), 127.8 (*o*-Ph), 128.7 (C3), 128.9 (*m*-CH_2Ph), 129.5 (*m*-Ph), 129.9 (*o*-CH_2Ph), 132.8 (*p*-Ph), 134.3 (C6), 134.6 (*i*-Ph), 139.6 (*i*-CH_2Ph), 157.8 (C2), 165.5 (CO), 166.7 (C2′); LRMS (ESI) *m*/*z* (%): 428.3 ([M+Na]$^+$, 100), 406.3 ([M+H]$^+$, 15), 412.3 ([M+Li]$^+$, 100). Anal. Calcd for $C_{23}H_{23}O_4N_3$: C, 68.13; H, 5.72; N, 10.36%. Found: C, 68.23; H, 5.71; N, 10.26%.

Acknowledgements

Financial support for this work was provided by (1) Natural Product Discovery, Griffith University and (2) the Eskitis Institute for Cell and Molecular Therapies, Griffith University.

Supplementary data

Supplementary data available: (a) general procedures and experimental procedures for compounds **1**–**4**; (b) ^1H NMR spectra for compounds **2**, **4**, **5**, **11**, and **15**. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.068.

References and notes

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