Synthesis Bicyclic Pyridones via Cyclocondensation of Heterocyclic Ketene Aminals with β-ketoester Enol Tosylates

Sheng-Jiao Yan, Yan-Fei Niu, Rong Huang, Jun Lin,*

Key Laboratory of Medicinal Chemistry for Natural Resource (Yunnan University), Ministry of Education, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China

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*Corresponding author. Tel.: 0086-871-5033215; fax: 0086-871-5033215; e-mail: linjun@ynu.edu.cn.
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**General Method**

All compounds were fully characterized by spectroscopic data. The NMR spectra were recorded on a Bruker DRX500 (1H: 500 MHz, 13C: 125 MHz, 19F: 470 MHz), chemical shifts (δ) are expressed in ppm, and J values are given in Hz, and deuterated DMSO-\(d_6\) or Acetone-\(d_6\) was used as solvent. IR spectra were recorded on a FT-IR Thermo Nicolet Avatar 360 using KBr pellet. The reactions were monitored by thin layer chromatography (TLC) using silica gel GF\(_{254}\). The melting points were determined on XT-4A melting point apparatus and are uncorrected. HRMs were performed on a Agilent LC/Msd TOF instrument.

All chemicals and solvents were used as received without further purification unless otherwise stated. Column chromatography was performed on silica gel (200–300 mesh).

The materials 1a–l were synthesized according to the literature.\(^1\) Compounds 1m–o were prepared according to the literature.\(^2\) 2a–b were obtained according to the literature.\(^3\)

![8-nitro-7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (4a): yellow solid; mp 201–203 °C. IR (KBr): 3440 (NH), 3351 (NH), 3111 (C=CH), 1687 (C=O), 1597 (C=C), 1339 (NO\(_2\)), 1273 (C-N), 1157 (C-F) cm\(^{-1}\). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): δ = 3.86–3.90 (m, 2H, CH\(_2\)), 4.09–4.13 (m, 2H, CH\(_2\)), 6.21 (s, 1H, CH=), 9.70 (br, 1H, NH). \(^13\)C NMR (125 MHz, DMSO-\(d_6\)): δ](image)
8-acetyl-7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (4b): yellow solid; mp 148–149.5 °C. IR (KBr): 3428 (NH), 3335 (NH), 3091 (C=CH), 1671 (C=O), 1608 (C=O), 1171 (C-N), 1031 (C-F) cm\(^{-1}\). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta = 2.34\) (s, 3H, CH\(_3\)), 3.74–3.78 (m, 2H, CH\(_2\)), 4.04–4.07 (m, 2H, CH\(_2\)), 6.00 (s, 1H, CH=), 8.72 (br, 1H, NH). \(^13\)C NMR (125 MHz, DMSO-\(d_6\)): \(\delta = 30.3\) (CH\(_3\)), 43.0 (NCH\(_2\)), 43.7 (NCH\(_2\)), 94.9 (CCOMe), 105.9 (CHCO), 123.2 (d, \(J = 272.5\) Hz, CF\(_3\)), 139.2 (q, \(J = 30\) Hz, CCF\(_3\)), 156.3 (C=C-COMe), 159.0 (C=O), 193.9 (COMe). HRMS (TOF ES\(^-\)) calcd for C\(_{10}\)H\(_8\)F\(_3\)N\(_2\)O\(_2\) [M-H\(^+\)], 245.0543; found, 245.0541.

ethyl 7-(trifluoromethyl)-1,2,3,5-tetrahydro-5-oxoimidazo[1,2-a]pyridine-8-carboxylate (4c): yellow solid; mp 177–179.5 °C. IR (KBr): 3363 (NH), 2981 (CH\(_3\)), 1672 (COOEt), 1634 (C=O), 1323 (C-N), 1269 (C-O), 1155 (C-F) cm\(^{-1}\). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta = 1.23\) (t, \(J = 7.0\) Hz, 3H, CH\(_3\)), 3.77–3.79 (m, 2H, CH\(_2\)), 4.05–4.07 (m, 2H, CH\(_2\)), 4.19 (q, \(J = 7.0\) Hz, 2H, CH\(_2\)), 5.97 (s, 1H, CH=), 8.41 (br, 1H, NH). \(^13\)C NMR (125 MHz, DMSO-\(d_6\)): \(\delta = 14.2\) (CH\(_3\)), 43.0 (NCH\(_2\)), 43.9 (NCH\(_2\)), 60.4 (OCH\(_2\)), 83.0 (CCOOEt), 106.3 (CHCO), 122.9 (q, \(J = 272.5\) Hz, CF\(_3\)), 140.1 (q, \(J = 31.3\) Hz, CCF\(_3\)), 157.2 (C=C-COOEt), 159.3(C=O), 164.0 (COOEt). HRMS (TOF ES\(^-\)) calcd for C\(_{11}\)H\(_{10}\)F\(_3\)N\(_2\)O\(_3\) [M-H\(^+\)], 275.0649; found, 275.0645.
8-benzoyl-7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (4e): yellow solid; mp 216–218 °C. IR (KBr): 3437 (NH), 3182 (NH), 3083 (C=CH), 1657 (C=O), 1549 (Ph), 1279 (C-N), 1157 (C-F) cm\(^{-1}\). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta = 3.64–3.67 \text{ (m, 2H, CH}_2\)), 4.08–4.12 (m, 2H, CH\(_2\)), 5.97 (s, 1H, CH=), 7.48–7.51 (m, 2H, PhH), 7.61–7.64 (br, 1H, NH), 7.72–7.76 (m, 2H, PhH). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)): \(\delta = 43.0 \text{ (NCH}_2\)), 44.2 (NCH\(_2\)), 92.5 (CCOPh), 104.4 (CHCO), 123.0 (d, \(J = 275 \text{ Hz, CF}_3\)), 128.8 (2 \times \text{ CH}_\text{ar}), 129.6 (2 \times \text{ CH}_\text{ar}), 133.4 (\text{CH}_\text{ar}), 138.8, 140.5 (d, \(J = 30 \text{ Hz, CCF}_3\)), 154.7 (C=C-COPh), 159.4 (C=O), 192.0 (COPh). HRMS (TOF ES\(^{-}\)) calcd for C\(_{15}\)H\(_{10}\)F\(_3\)N\(_2\)O\(_2\) [M-H\(^+\)], 307.0700; found, 307.0701.

8-(4-methylbenzoyl)-7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (4f): yellow solid; mp 196–198 °C. IR (KBr): 3433 (NH), 3270 (NH), 1658 (C=O), 1548 (Ar), 1277 (C-N), 1195 (C-F) cm\(^{-1}\). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta = 2.38 \text{ (s, 3H, CH}_3\)), 3.63 (t, \(J = 9.1 \text{ Hz, 2H, CH}_2\)), 4.09 (t, \(J = 9.1 \text{ Hz, 2H, CH}_2\)), 5.96 (s, 1H, CH=), 7.30 (d, \(J = 7.8 \text{ Hz, 2H, ArH}\)), 7.62 (br, 1H, NH), 7.66 (d, \(J = 7.9 \text{ Hz, 2H, ArH}\)). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)): \(\delta = 21.1 \text{ (ArCH}_3\)), 42.5 (NCH\(_2\)), 43.7 (NCH\(_2\)), 92.2 (CCOAr), 103.5 (CHCO), 121.6 (d, \(J = 273.8 \text{ Hz, CF}_3\)), 129.0 (2 \times \text{ CH}_\text{ar}), 129.4 (2 \times \text{ CH}_\text{ar}), 135.5 (\text{C}_\text{ar}), 140.1 (q, \(J = 31.2 \text{ Hz, CCF}_3\)), 143.5 (\text{C}_\text{ar}), 153.9 (C=C-COAr), 158.9 (C=O), 191.1 (COAr). HRMS (TOF ES\(^{-}\)) calcd for C\(_{16}\)H\(_{12}\)F\(_3\)N\(_2\)O\(_2\) [M-H\(^+\)], 321.0856; found, 321.0852.
8-(4-methoxybenzoyl)-7-(trifluoromethyl)-2,3-dihydroimidazo[1,2-a]pyridin-5(1H)-one (4g):
yellow solid; mp 219–220 °C. IR (KBr): 3437 (NH), 3181 (NH), 1654 (C=O), 1596 (Ar), 1548 (Ar),
1470 (Ar), 1268 (C-N), 1152 (C-F) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 3.63 (t, J = 9.1 Hz,
2H, CH₂), 3.85 (s, 3H, CH₃), 4.09 (t, J = 9.1 Hz, 2H, CH₂), 5.94 (s, 1H, CH=), 7.02 (d, J = 8.7 Hz,
2H, ArH), 7.51 (br, 1H, NH), 7.76 (d, J = 8.7 Hz, 2H, ArH). ¹³C NMR (125 MHz, DMSO-d₆): δ =
42.9 (NCH₂), 44.2 (NCH₂), 55.9 (OCH₃), 92.8 (CCOAr), 103.7 (CHCO), 114.2 (2 × CH₆), 123.1
(q, J = 275.0 Hz, CBr₃), 131.0 (CH₆), 132.2 (2 × CH₆), 140.6 (q, J = 31.3 Hz, CCF₃), 154.1
(C=C-COAr), 159.4 (C=O), 163.8 (C₆), 190.4 (COAr). HRMS (TOF ES⁺) calcd for C₁₆H₁₄F₃N₂O₃
[M+H⁺], 339.0951; found, 339.0948.

8-acetyl-2,3-dihydro-7-methylimidazo[1,2-a]pyridin-5(1H)-one (4h): yellow solid; mp
216–218 °C. IR (KBr): 3425 (NH), 3327 (NH), 2968 (CH₃), 1659 (C=O), 1591 (C=O), 1369 (C-N)
cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 2.35 (s, 3H, CH₃), 2.39 (s, 3H, CH₃), 3.72–3.76 (m, 2H,
CH₂), 3.94–3.98 (m, 2H, CH₂), 5.46 (s, 1H, CH=), 9.05 (br, 1H, NH). ¹³C NMR (125 MHz,
DMSO-d₆): δ = 23.9 (CH₃), 32.1 (COCH₃), 42.3 (NCH₂), 42.5 (NCH₂), 99.0 (CCOMe), 107.4
(CHCO), 151.5 (CCH₃), 156.5 (C=C-COMe), 159.3 (C=O), 193.9 (COMe). HRMS (TOF ES⁺)
calcd for C₁₀H₁₃N₂O₂ [M+H⁺], 193.0972; found, 193.0972.
8-(4-chlorobenzoyl)-2,3-dihydro-7-methylimidazo[1,2-a]pyridin-5(1H)-one (4i): yellow solid; mp 178−182 °C. IR (KBr): 3429 (NH), 3291 (NH), 1664 (C=O), 1596 (Ar), 1365 (C-N) cm⁻¹. ¹H NMR (500 MHz, DMSO-­d₆): δ = 1.66 (s, 3H, CH₃), 3.75−3.77 (m, 2H, CH₂), 4.01−4.05 (m, 2H, CH₂), 5.47 (s, 1H, CH=), 7.49−7.53 (m, 4H, ArH), 8.44 (br, 1H, NH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 22.8 (CH₃), 42.5 (NCH₂), 42.9 (NCH₂), 97.4 (COAr), 107.4 (CHCO), 128.4 (2 × CHₐr), 129.5 (2 × CHₐr), 135.5 (Cₐr), 140.8 (Cₐr), 150.7 (CH₃), 156.1 (C=C-COAr), 159.6 (C=O). HRMS (TOF ES⁺) calcd for C₁₅H₁₄ClN₂O₂ [M+H⁺], 289.0738; found, 289.0745.

![Chemical structure of 8-(4-chlorobenzoyl)-2,3-dihydro-7-methylimidazo[1,2-a]pyridin-5(1H)-one](image)

8-benzoyl-2,3-dihydro-7-methylimidazo[1,2-a]pyridin-5(1H)-one (4j): yellow solid; mp 184−186 °C. IR (KBr): 3425 (NH), 3289 (NH), 2972 (CH₃), 1664 (C=O), 1597 (Ph), 1363 (C-N) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 1.62 (s, 3H, CH₃), 3.75 (t, J = 9.4 Hz, 2H, CH₂), 4.04 (t, J = 9.3 Hz, 2H, CH₂), 5.45 (s, 1H, CH=), 7.46−7.51 (m, 5H, PhH), 8.45 (br, 1H, NH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 23.2 (CH₃), 43.0 (NCH₂), 43.4 (NCH₂), 98.0 (CCOPh), 107.7 (CHCO), 127.9 (2 × CHₐr), 128.7 (2 × CHₐr), 131.2 (CHₐr), 142.7 (CCH₃), 151.3 (Cₐr), 156.5 (C=C-COPh), 160.0 (C=O), 193.2 (COPh). HRMS (TOF ES⁺) calcd for C₁₅H₁₅N₂O₂ [M+H⁺], 255.1128; found, 255.1133.

![Chemical structure of 8-benzoyl-2,3-dihydro-7-methylimidazo[1,2-a]pyridin-5(1H)-one](image)

8-(4-methylbenzoyl)-2,3-dihydro-7-methylimidazo[1,2-a]pyridin-5(1H)-one (4k): yellow solid; mp 203 °C. IR (KBr): 3305 (NH), 1663 (C=O), 1599 (Ar), 1363 (C-N), 1332 (C-N) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 1.66 (s, 3H, CH₃), 2.36 (s, 3H, CH₃), 3.70−3.74 (m, 2H, CH₂), 4.00−4.04 (m, 2H, CH₂), 5.45 (s, 1H, CH=), 7.26 (d, J = 7.8 Hz, 2H, ArH), 7.39 (d, J = 7.8 Hz, 2H, ArH), 8.25 (br, 1H, NH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 21.4 (CH₃), 23.1 (ArCH₃), 42.9
(NCH₂), 43.4 (NCH₂), 98.1 (CCOAr), 107.4 (CHCO), 128.3 (2 × CH₅), 129.3 (2 × CH₅), 139.6 (C₆), 141.5 (C₆), 151.4 (C₆H₃), 156.2 (C=C-COAr), 160.0 (C=O), 193.2 (COAr). HRMS (TOF ES⁺) calcd for C₁₆H₁₇N₂O₂ [M+H⁺], 269.1285; found, 269.1289.

8-(4-methoxybenzoyl)-2,3-dihydro-7-methylimidazo[1,2-a]pyridin-5(1H)-one (4l): yellow solid; mp 179–180 °C. IR (KBr): 3409 (NH), 1659 (C=O), 1599 (Ar), 1318 (C-N), 1257 (C-O) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 1.72 (s, 3H, CH₃), 3.68–3.71 (m, 2H, CH₂), 3.82 (s, 3H, CH₃), 4.00–4.04 (m, 2H, CH₂), 5.45 (s, 1H, CH=), 7.00 (d, J = 8.6 Hz, 2H, ArH), 7.51 (d, J = 8.6 Hz, 2H, ArH), 8.00 (br, 1H, NH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 22.3 (CH₃), 42.4 (NCH₂), 43.1 (NCH₂), 55.3 (OCH₃), 97.6 (CCOAr), 106.7 (CHCO), 113.6 (2 × CH₅), 130.2 (2 × CH₅), 133.8 (C₆), 150.8 (C₆H₃), 155.3 (C=C-COAr), 159.5 (C=O), 161.8 (C₆), 191.9 (COAr). HRMS (TOF ES⁺) calcd for C₁₆H₁₇N₂O₃ [M+H⁺], 285.1234; found, 285.1232.

9-(4-fluorobenzoyl)-8-(trifluoromethyl)-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidin-6-one (5a): yellow solid; mp 218–219 °C. IR (KBr): 3437 (NH), 1675 (C=O), 1600 (Ar), 1146 (Ar-F) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 1.95 (s, 3H, CH₃), 3.20 (s, 2H, CH₂), 3.93 (s, 2H, CH₂), 5.90 (s, 1H, CH=), 7.29–7.84 (m, 5H, ArH, NH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 19.2 (CH₂), 39.9 (NCH₂), 40.0 (NCH₂), 94.4 (CCOAr), 99.9 (CHCO), 115.8 (d, J = 21.2 Hz, CCF₃), 123.0 (d, J = 275 Hz, CF₃), 132.8 (d, J = 8.8 Hz, C₆), 135.6 (d, J = 55 Hz, 2 × CH₅), 138.8 (d, J = 31.2 Hz, 2 × CH₅), 150.9 (C=C-COAr), 160.5 (C=O), 165.4 (d, J = 250 Hz, C₆), 192.0 (COAr). HRMS (TOF ES⁻) calcd for C₁₆H₁₁F₄N₂O₂ [M-H⁻], 339.0762; found, 339.0767.
9-(4-chlorobenzoyl)-8-(trifluoromethyl)-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidin-6-one (5b): yellow solid; mp 196–199 °C. IR (KBr): 3428 (NH), 3325 (NH), 3087 (C=CH), 1677 (C=O), 1606 (Ar), 1333 (C-N), 1165 (C-N) cm⁻¹. ¹H NMR (500 MHz, DMSO-dma): δ = 1.94 (s, 2H, CH₂), 3.20 (s, 2H, CH₂), 3.93 (t, J = 5.65 Hz, 2H, CH₂), 5.92 (s, 1H, CH=), 7.55 (d, J = 8.5 Hz, 2H, ArH), 7.76 (d, J = 8.5 Hz, 2H, ArH), 7.82 (br, 1H, NH). ¹³C NMR (125 MHz, DMSO-dma): δ = 19.1 (CH₂), 39.7 (NCH₂), 40.0 (NCH₂), 94.2 (CCOAr), 100.2 (CHCO), 123.0 (d, J = 278 Hz, CF₃), 128.9 (2 × CH₃), 131.6 (2 × CH₃), 137.9 (C₆H₅), 138.3 (C₆H₅), 138.9 (q, J = 31.3 Hz, CCF₃), 151.1 (C=COAr), 160.5 (C=O), 192.2 (COAr). HRMS (TOF ES⁻) calcd for C₁₆H₁₁ClF₃N₂O₂ [M-H⁻], 355.0467; found, 355.0467.

9-benzoyl-8-(trifluoromethyl)-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidin-6-one (5c): yellow solid; mp 208–211 °C. IR (KBr): 3431 (NH), 1677 (C=O), 1607 (Ph), 1147 (C-F) cm⁻¹. ¹H NMR (500 MHz, DMSO-dma): δ = 1.99 (s, 2H, CH₂), 3.25 (s, 2H, CH₂), 3.98 (s, 2H, CH₂), 5.94 (s, 1H, CH=), 7.52–7.80 (m, 6H, PhH, NH). ¹³C NMR (125 MHz, DMSO-dma): δ = 20.6 (CH₂), 41.0 (NCH₂), 41.7 (NCH₂), 95.9 (CCOPh), 101.2 (CHCO), 125.5 (CF₃), 130.2 (2 × CH₃), 131.1 (2 × CH₃), 134.9 (CH₃), 140.6 (CCF₃), 152.3 (C=COOPh), 161.9 (C=O), 194.9 (COAr). HRMS (TOF ES⁻) calcd for C₁₆H₁₂F₃N₂O₂ [M-H⁻], 321.0856; found, 321.0859.
9-(4-methylbenzoyl)-8-(trifluoromethyl)-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidin-6-one (5d): yellow solid; mp 205–207 °C. IR (KBr): 3372 (NH), 3074 (C=CH), 1672 (C=O), 1611 (Ar), 1285 (C-N), 1148 (C-F) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 1.92–1.94 (m, 2H, CH₂), 2.38 (s, 3H, CH₃), 3.20 (s, 2H, CH₂), 3.92–3.04 (m, 2H, CH₂), 5.88 (s, 1H, CH=), 7.29 (d, J = 8.1 Hz, 2H, ArH), 7.59 (br, 1H, NH), 7.67 (d, J = 8.0 Hz, 2H, ArH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 19.2 (CH₂), 21.5 (ArCH₃), 39.7 (NCH₂), 40.0 (NCH₂), 94.8 (C=O), 123.0 (d, J = 205.0 Hz, CF₃), 129.4 (2 × CH₃), 129.9 (2 × CH₃), 136.4 (C₆H₃), 138.8 (d, J = 31.5 Hz, CCF₃), 144.1 (C₆H₅), 150.6 (C=COAr), 160.5 (C-O), 193.1 (COAr). HRMS (TOF ES⁻) calcd for C₁₇H₁₄F₃N₂O₂ [M-H⁻], 335.1013; found, 335.1013.

9-(4-methoxybenzoyl)-8-(trifluoromethyl)-1,2,3,4-tetrahydropyrido[1,2-a]pyrimidin-6-one (5e): yellow solid; mp 184–186 °C. IR (KBr): 3421 (NH), 3247 (NH), 1658 =C=O), 1595 (C=O), 1595 (Ar), 1269 (C-N), 1156 (C-F) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 1.92–1.94 (m, 2H, CH₂), 2.38–3.19 (m, 2H, CH₂), 3.85 (s, 3H, CH₃), 3.93 (m, 2H, CH₂), 5.85 (s, 1H, CH=), 7.01 (d, J = 8.8 Hz, 2H, ArH), 7.36 (br, 1H, NH), 7.75 (d, J = 8.7 Hz, 2H, ArH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 19.3 (CH₂), 39.5 (NCH₂), 40.2 (NCH₂), 55.9 (OCH₃), 95.1 (C=O), 98.8 (CHCO), 114.1 (2 × CH₃), 123.1 (d, J = 275.0 Hz, CF₃), 131.6 (C₆H₅), 132.3 (2 × CH₃), 138.6 (d, J = 30.0 Hz, CCF₃), 150.3 (C=COAr), 160.5 (C=O), 163.8 (C₆H₅), 192.0 (COAr). HRMS (TOF ES⁻) calcd for C₁₇H₁₄F₃N₂O₃ [M-H⁻], 351.0962; found, 351.0961.
9-(4-chlorobenzoyl)-1,2,3,4-tetrahydro-8-methylpyrido[1,2-\(a\)]pyrimidin-6-one (5f): yellow solid; mp 144–146 °C. IR (KBr): 3425 (NH), 1668 (C=O), 1582 (Ar), 1338 (C-N), 1258 (C-N) cm\(^{-1}\). \(^1\)H NMR (500 MHz, DMSO-\(d_6\)): \(\delta = 1.56\) (s, 3H, CH\(_3\)), 1.95–1.97 (m, 2H, CH\(_2\)), 3.41 (s, 2H, CH\(_2\)), 3.89–3.91 (m, 2H, CH\(_2\)) 5.50 (s, 1H, CH=), 7.45–7.52 (m, 4H, ArH), 10.14 (br, 1H, NH). \(^{13}\)C NMR (125 MHz, DMSO-\(d_6\)): \(\delta = 19.0\) (CH\(_2\)), 24.3 (CH\(_3\)), 39.0 (NCH\(_2\)), 39.5 (NCH\(_2\)), 98.7 (C-COAr), 106.2 (CHCO), 128.8 (2 \times CH\(_{ar}\)), 130.0 (2 \times CH\(_{ar}\)), 135.8 (C\(_{ar}\)), 142.2 (C\(_{ar}\)) 150.4 (CCH\(_3\)), 153.9 (C=C-COAr), 160.5 (C=O), 192.8 (COAr). HRMS (TOF ES\(^+\)) calcd for C\(_{16}\)H\(_{16}\)ClN\(_2\)O\(_2\) [M+H\(^+\)], 303.0895; found, 303.0900.

9-benzoyl-1,2,3,4-tetrahydro-8-methylpyrido[1,2-\(a\)]pyrimidin-6-one (5g): yellow solid; mp 154–156 °C. IR (KBr): 3429 (NH), 3066 (C=CH), 1665 (C=O), 1574 (Ar), 1264 (C-N) cm\(^{-1}\). \(^1\)H NMR (500 MHz, Acetone-\(d_6\)): \(\delta = 1.60\) (s, 3H, CH\(_3\)), 2.10–2.14 (m, 2H, CH\(_2\)), 3.56–3.59 (m, 2H, CH\(_2\)), 4.00–4.03 (m, 2H, CH\(_2\)), 5.50 (s, 1H, CH=), 7.44–7.53 (m, 5H, PhH), 10.56 (br, 1H, NH). \(^{13}\)C NMR (125 MHz, Acetone-\(d_6\)): \(\delta = 20.5\) (CH\(_2\)), 24.9 (CH\(_3\)), 39.8 (NCH\(_2\)), 40.3 (NCH\(_2\)), 99.8 (CCOPh), 107.5 (CHCO), 129.1 (2 \times CH\(_{ar}\)), 129.5 (2 \times CH\(_{ar}\)), 131.7 (CH\(_{ar}\)), 145.4 (CH\(_{ar}\)), 151.8 (CCH\(_3\)), 155.7 (C=C-COPh), 161.6 (C=O), 195.6 (COPh). HRMS (TOF ES\(^-\)) calcd for C\(_{16}\)H\(_{15}\)N\(_2\)O\(_2\) [M-H\(^-\)], 267.1139; found, 267.1140.
9-(4-methylbenzoyl)-1,2,3,4-tetrahydro-8-methylpyrido[1,2-a]pyrimidin-6-one (5h): yellow solid; mp 198–200 °C. IR (KBr): 3429 (NH), 1663 (C=O), 1578 (Ar), 1256 (C-N) cm⁻¹. ¹H NMR (500 MHz, DMSO-$_d6$): $\delta = 1.56$ (s, 3H, CH$_3$), 1.94–1.96 (m, 2H, CH$_2$), 2.36 (s, 3H, CH$_3$), 3.39 (s, 2H, CH$_2$), 3.88–3.91 (m, 2H, CH$_2$), 5.48 (s, 1H, CH=), 7.25–7.37 (m, 4H, ArH), 9.90 (br, 1H, NH). ¹³C NMR (125 MHz, DMSO-$_d6$): $\delta = 19.2$ (CH$_2$), 21.4 (CH$_3$), 24.0 (ArCH$_3$), 38.7 (NCH$_2$), 39.7 (NCH$_2$), 99.0 (COCOAr), 105.6 (CHCO), 128.4 ($2 \times$ CH$_{ar}$), 129.3 ($2 \times$ CH$_{ar}$), 140.6 (C$_{ar}$), 141.3 (C$_{ar}$), 150.7 (CCH$_3$), 153.5 (C=C-COAr), 160.5 (C=O), 194.3 (COAr). HRMS (TOF ES⁺) calcd for C$_{17}$H$_{19}$N$_2$O$_2$ [M+H⁺], 283.1441; found, 283.1443.

9-(4-methoxybenzoyl)-1,2,3,4-tetrahydro-8-methylpyrido[1,2-a]pyrimidin-6-one (5i): yellow solid; mp 164–165 °C. IR (KBr): 3428 (NH), 1664 (C=O), 1595 (Ar), 1259 (C-N), 1167 (C-O) cm⁻¹. ¹H NMR (500 MHz, Acetone-$_d6$): $\delta = 1.67$ (s, 3H, CH$_3$), 2.07–2.11 (m, 2H, CH$_2$), 3.51–3.53 (m, 2H, CH$_2$), 3.88 (s, 3H, CH$_3$), 3.99–4.01 (m, 2H, CH$_2$), 5.49 (s, 1H, CH=), 6.99 (d, $J = 8.7$, 2H, ArH), 7.50 (d, $J = 8.7$, 2H, ArH), 9.96 (br, 1H, NH). ¹³C NMR (125 MHz, Acetone-$_d6$): $\delta = 20.6$ (CH$_2$), 24.6 (CH$_3$), 39.8 (NCH$_2$), 40.3 (NCH$_2$), 56.2 (OCH$_3$), 99.9 (COCOAr), 106.8 (CHCO), 114.7 ($2 \times$ CH$_{ar}$), 131.5 ($2 \times$ CH$_{ar}$), 137.2 (C$_{ar}$), 151.7 (CCH$_3$), 155.0 (C=C-COAr), 161.7 (C=O), 163.5 (C$_{ar}$), 194.9 (COAr). HRMS (TOF ES⁻) calcd for C$_{17}$H$_{17}$N$_2$O$_3$ [M-H⁻], 297.1245; found, 297.1245.
8-benzoyl-7-(trifluoromethyl)-2,3-dihydrooxazolo[3,2-a]pyridin-5-one (6a): yellow solid; mp 196–198 °C. IR (KBr): 3437 (NH), 1673 (C=O), 1612 (Ar), 1281 (C-N), 1190 (C-F), 1142 (C-O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 4.26$ (t, $J = 8.6$ Hz, 2H, CH$_2$), 4.73 (t, $J = 8.6$ Hz, 2H, CH$_2$), 6.52 (s, 1H, CH=), 7.46–7.51 (m, 5H, PhH). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 44.2$ (NCH$_2$), 71.0 (OCH$_2$), 94.0 (CCOPh), 110.1 (CHCO), 119.5–123.8 (m, CF$_3$), 129.0 (2 × CH$_{ar}$), 129.8 (2 × CH$_{ar}$), 134.1 (C$_{ar}$), 137.7 (C$_{ar}$), 140.9 (d, $J = 31.3$ Hz, CCF$_3$), 158.2 (C=C-COPh), 158.5 (C=O), 189.9 (COPh). HRMS (TOF ES$^+$) calcd for C$_{15}$H$_{11}$F$_3$NO$_3$ [M+H$^+$], 310.0686; found, 310.0685.

8-(4-methylbenzoyl)-7-(trifluoromethyl)-2,3-dihydrooxazolo[3,2-a]pyridin-5-one (6b): yellow solid; mp 178–179 °C. IR (KBr): 3428 (NH), 1669 (C=O), 1608 (Ar), 1283 (C-N), 1171 (C-F), 1133 (C-O) cm$^{-1}$. $^1$H NMR (500 MHz, DMSO-$d_6$): $\delta = 2.39$ (s, 3H, CH$_3$), 4.21 (t, $J = 8.4$ Hz, 2H, CH$_2$), 4.68 (t, $J = 8.5$ Hz, 2H, CH$_2$), 6.46 (s, 1H, CH=), 7.32 (d, $J = 7.8$ Hz, 2H, ArH), 7.79 (d, $J = 7.7$ Hz, 2H, ArH). $^{13}$C NMR (125 MHz, DMSO-$d_6$): $\delta = 21.6$ (ArCH$_3$), 44.2 (NCH$_2$), 70.9 (OCH$_2$), 94.1 (CCOAr), 109.9 (CHCO), 122.7 (d, $J = 273.8$ Hz, CF$_3$), 129.6 (2 × CH$_{ar}$), 130.0 (2 × CH$_{ar}$), 135.1 (C$_{ar}$), 140.9 (q, $J = 32.5$ Hz, CCF$_3$), 144.8 (C$_{ar}$), 158.0 (C=C-COAr), 158.5 (C=O), 189.4 (COAr). HRMS (TOF ES$^+$) calcd for C$_{16}$H$_{13}$F$_3$NO$_3$ [M+H$^+$], 324.0842; found, 324.0840.
8-(4-methoxybenzoyl)-7-(trifluoromethyl)-2,3-dihydrooxazolo[3,2-a]pyridin-5-one (6c): yellow solid; mp 174–175.5 °C. IR (KBr): 3429 (NH), 1686 (C=O), 1653 (C=O), 1605 (Ar), 1274 (C-N), 1169 (C-F), 1149 (C-O) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 3.91 (s, 3H, CH₃), 4.27 (t, J = 8.5 Hz, 2H, CH₂), 4.74 (t, J = 8.5 Hz, 2H, CH₂), 6.49 (s, 1H, CH=), 7.07 (d, J = 8.8 Hz, 2H, ArH), 7.92 (d, J = 8.7 Hz, 2H, ArH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 44.2 (NCH₂), 56.0 (OCH₃), 70.8 (OCH₂), 94.2 (CCOAr), 109.8 (CHCO), 114.4 (2 × CH₃), 122.8 (d, J = 273.8 Hz, CF₃), 130.4 (C₆), 132.4 (2 × CH₃), 140.9 (d, J = 32.5 Hz, CCF₃), 157.7 (C=C-COAr), 158.5 (C=O), 164.1 (C₆), 188.3 (COAr). HRMS (TOF ES⁺) calcd for C₁₆H₁₃F₃NO₄ [M+H⁺], 340.0791; found, 340.0793.

8-benzoyl-2,3-dihydro-7-methyloxazolo[3,2-a]pyridin-5-one (6d): yellow solid; mp 194–196 °C. IR (KBr): 3433 (NH), 1670 (C=O), 1638 (C=O), 1300 (C-N), 1064 (C-O) cm⁻¹. ¹H NMR (500 MHz, DMSO-d₆): δ = 2.15 (s, 3H, CH₃), 4.14 (t, J = 8.1 Hz, 2H, CH₂), 4.60 (t, J = 8.1 Hz, 2H, CH₂), 5.93 (s, 1H, CH=), 7.47–7.79 (m, 5H, PhH). ¹³C NMR (125 MHz, DMSO-d₆): δ = 20.7 (CH₃), 43.7 (NCH₂), 70.0 (OCH₂), 98.3 (CCOPh), 111.2 (CHCO), 128.8 (2 × CH₃), 129.5 (2 × CH₃), 133.2 (C₆), 139.2 (C₆), 152.9 (CH₃), 158.1 (C=C-COPh), 159.2 (C=O), 191.7 (COPh). HRMS (TOF ES⁺) calcd for C₁₅H₁₃NNaO₃ [(M+Na⁺)], 278.0788; found, 278.0794.

**Biological results and discussion**
The cytotoxic potential of all newly synthesized bicyclic pyridones were evaluated in vitro against a panel of human tumor cell lines according to procedures described in the literature. The tumor cell line panel consisted of myeloid leukaemia (HL-60 and K562), epidermoid carcinoma (A431), ovarian carcinoma (Skov-3), laryngeal carcinoma (Hep-2). Cisplatin (DDP) was used as the reference drug. The results of the cytotoxicity studies were summarized in Table 2~3 (IC₅₀ value, defined as the concentrations corresponding to 50% growth inhibition). As shown in Table 2~3, the cytotoxic activities of 4a–g with trifluoromethyl substituent at position-7 of bicyclic pyridones is 4c > 4g > 4f > 4d > 4b > 4a, the results showed that substitution of the position-8 with an electron-rich substituted group played a vital role in the modulation of the cytotoxic activities. Among them, compound 4c, bearing ethoxycarbonyl substituents, was the most active. The cytotoxicity to tumor cell lines of the methyl substituted 5,6-ring bicyclic pyridones 4h–l compliance with the laws as 4a–g. The 6,6-ring bicyclic pyridones 5a–e with trifluoromethyl substituent at position-8 of pyridones comply with the rule of compounds 4. It shown that 5d and 5e is more active to tumor cell lines. However, The methyl substituted 6,6-ring bicyclic pyridones 5f–i, In contrast with the law as compounds 4 and 5a–e. Compared with all bicyclic pyridones derivatives 4–6, 6b–e has the most remarkable activity to the tumor cell line HepG2, A431 and A459. Compound 6c was found to be the most potent derivative with IC₅₀ values lower than 1.0µg/ml against 3 strains human tumor cell lines and more active than that of DDP.

So 6c can be considered promising leads for further structural modifications guided by the valuable information derivable from our detailed SARs.

Table 2. Cytotoxic activities of bicyclic pyridones in vitro (IC₅₀, µg/ml)

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* Cytotoxicity as IC₅₀, for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay.

* Data represent the mean values of three independent determinations.

Table 3. Cytotoxic activities of bicyclic pyridones in vitro (IC₅₀, µg/ml)

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* Cytotoxicity as IC₅₀ for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay.
* Data represent the mean values of three independent determinations.

**Figure 1** ¹H NMR (500 MHz, DMSO-d₆) spectra of compound 4a
Figure 2 $\text{^{13}C NMR (125 MHz, DMSO-}d_6\text{) spectra of compound 4a}$

Figure 3 $\text{^1H NMR (500 MHz, DMSO-}d_6\text{) spectra of compound 4b}$
Figure 4  $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 4b

Figure 5  $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 4c
Figure 6  $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 4c

Figure 7  $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 4d
Figure 8 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 4d
Figure 9  $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 4e

Figure 10  $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 4e

Figure 11  $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 4f
Figure 12 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 4f
Figure 13 $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 4g

Figure 14 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 4g
Figure 15 $^1$H NMR (500 MHz, DMSO-$_d_6$) spectra of compound 4h

Figure 16 $^{13}$C NMR (125 MHz, DMSO-$_d_6$) spectra of compound 4h
Figure 17 $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 4i

Figure 18 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 4i
Figure 19  $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 4j

Figure 20  $^1$H NMR (125 MHz, DMSO-$d_6$) spectra of compound 4j
Figure 21 $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 4k

Figure 22 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 4k
Figure 23 $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 41
Figure 24  $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 4l

Figure 25  $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 5a

Figure 26  $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 5b
Figure 27 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 5b

Figure 28 $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 5c
Figure 29 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 5c

Figure 30 $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 5d
Figure 31 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 5d

Figure 32 $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 5e
Figure 33 $^{13}$C NMR (125 MHz, DMSO-d$_6$) spectra of compound 5e

Figure 34 $^1$H NMR (500 MHz, DMSO-d$_6$) spectra of compound 5f
Figure 35 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 5f

Figure 36 $^1$H NMR (500 MHz, Acetone-$d_6$) spectra of compound 5g
Figure 37  $^{13}$C NMR (125 MHz, Acetone-$_{d_6}$) spectra of compound 5g

Figure 38  $^1$H NMR (500 MHz, DMSO-$_{d_6}$) spectra of compound 5h
Figure 39 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 5h

Figure 40 $^1$H NMR (500 MHz, Acetone-$d_6$) spectra of compound 5i
Figure 41  $^{13}$C NMR (125 MHz, Acetone-$d_6$) spectra of compound 5i

Figure 42  $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 6a
Figure 43 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 6a

Figure 44 $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 6b
Figure 45 $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 6b

Figure 46 $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 6c
Figure 47  $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 6c

Figure 48  $^1$H NMR (500 MHz, DMSO-$d_6$) spectra of compound 6d
Figure 49  $^{13}$C NMR (125 MHz, DMSO-$d_6$) spectra of compound 6d
References


