

7.3 Ugi type three component reaction

General procedure for Ugi-type reaction with 2-aminopyridine

U2-AP

Dry methanol was placed into a flame-dried flask under an argon atmosphere. Siloxycyclopropanecarboxylate, amine and isocyanide were added to the reaction vessel, followed by addition of acetic acid. The reaction mixture was stirred under argon for 19-48 hours. 1 M HCl solution was added to adjust pH 1, the mixture was stirred for 30 min to destroy unreacted isocyanide and then evaporated to dryness. The residue was taken up in saturated aqueous NaHCO₃ solution and extracted with ethyl acetate. The combined organic phases were dried with Na₂SO₄ and the solvent was removed under reduced pressure.

Synthesis of Methyl 3-[3-(Benzylamino)imidazo[1,2-*a*]pyridin-2-yl]propanoate (95a)

E 18 (IV 54)

Starting amounts:

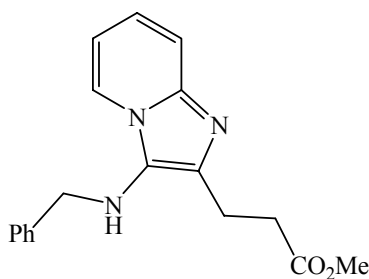
0.376 g (2.00 mmol) Siloxycyclopropanecarboxylate **53**
0.188 g (2.00 mmol) 2-Aminopyridine
0.236 g (2.00 mmol) Benzylisocyanide
6 ml MeOH, dry
0.250 g (4.00 mmol) Acetic acid 96 %

Procedure according to **U2-AP**

Reaction time: 24 hours

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2, then HPLC (20 % *i*-propanol/hexane, 64 ml/min, 95 bar)

Yield: 211 mg (33 %) of **95a** as yellow oil

**95a**

¹H-NMR (250 MHz, CDCl₃): δ = 2.65–2.81 (m, 4 H, CH₂), 3.60 (s, 3 H, OMe), 3.90 (t, J = 5.8 Hz, 1 H, NH), 4.10 (d, J = 5.8 Hz, 2 H, CH₂Ph), 6.69 (td, J = 6.7, 1.2 Hz, 1 H, 6-H), 7.04 (ddd, J = 9.0, 6.7, 1.2 Hz, 1 H, 7-H), 7.19–7.36 (m, 5 H, Ph), 7.40 (dt, J = 9.0, 1.2 Hz, 1 H, 8-H), 7.96 (dt, J = 6.7, 1.2 Hz, 1 H, 5-H).

¹³C-NMR (62.9 MHz, CDCl₃): δ = 21.8, 33.1 (2 t, CH₂), 51.4 (q, OMe), 52.7 (t, CH₂Ph), 111.0 (d, C-6), 116.7 (d, C-8), 122.1 (d, C-5), 123.0 (d, C-7), 125.9 (s, C-3), 126.8, 128.2, 128.4 (3 d, Ph), 136.8 (s, Ph), 139.4 (s, C-2), 141.2 (s, C-8a), 173.9 (s, C=O).

IR (KBr): ν = 3340–3225 cm⁻¹ (N-H), 3060–2850 (C-H), 1735 (C=O), 1635 (C=N).

MS (EI, 80 eV, 150 °C): m/z (%) = 309 (27, [M]⁺), 219 (14), 218 (100), 191 (15), 186 (10), 159 (10), 135 (12), 131 (12), 91 (20), 78 (47).

HRMS (EI, 80 eV) m/z calculated for [M]⁺: 309.14772, found: 309.14593.

C ₁₈ H ₁₉ N ₃ O ₂ ·1/2H ₂ O (318.4)	calc.	C 67.92	H 6.33	N 13.20
	found	C 67.97	H 5.71	N 12.61

Synthesis of Methyl 3-{3-[(1,1,3,3-Tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}propanoate (**95b**)

Starting amounts:

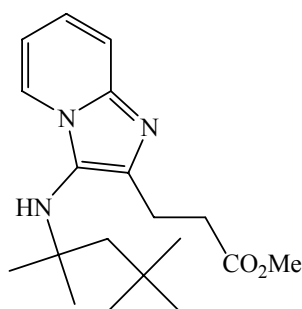
- 0.827 g (4.40 mmol) Siloxycyclopropanecarboxylate **53**
- 0.376 g (4.00 mmol) 2-Aminopyridine
- 0.558 g (4.00 mmol) 1,1,3,3-Tetramethylbutylisocyanide
- 12 ml MeOH, dry
- 0.500 g (8.00 mmol) Acetic acid 96 %

Procedure according to **U2-AP**

Reaction time: 48 hours

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 1.068 g (79 %) of **95b** as yellowish oil



95b

¹H-NMR (250 MHz, CDCl₃): δ = 1.05, 1.12 (2 s, 9 H, 6 H, Me), 1.64 (s, 2 H, CH₂), 2.76 (t, J = 6.8 Hz, 2 H, CH₂), 3.01 (t, J = 6.8 Hz, 2 H, CH₂), 3.21 (bs, 1 H, NH), 3.56 (s, 3 H, OMe), 6.63 (td, J = 6.8, 1.2 Hz, 1 H, 6-H), 6.86 (ddd, J = 9.0, 6.8, 1.2 Hz, 1 H, 7-H), 7.34 (dt, J = 9.0, 1.2 Hz, 1 H, 8-H), 8.11 (dt, J = 6.8, 1.2 Hz, 1 H, 5-H).

¹³C-NMR (125.8 MHz, CDCl₃): δ = 22.8 (t, CH₂), 29.1 (q, Me), 31.7 (s, CMe₃), 31.9 (q, Me), 33.3 (t, CH₂), 51.4 (q, OMe), 56.8 (t, CH₂), 59.5 (s, NCMe₂), 110.6 (d, C-6), 116.6 (d, C-8), 123.2 (d, C-7), 123.5 (d, C-5), 123.8 (s, C-3), 139.2 (s, C-2), 142.0 (s, C-8a), 173.9 (s, C=O).

IR (KBr): ν = 3335 cm⁻¹ (N-H), 3090–2870 (C-H), 1735 (C=O), 1630 (C=N).

MS (EI, 80 eV, 70 °C): m/z (%) = 331 (27, $[M]^+$), 220 (14), 219 (100), 218 (79), 186 (22), 161 (12), 160 (71), 159 (16), 158 (12), 146 (21), 131 (16), 119 (11), 85 (53), 84 (71), 79 (11), 78 (40), 57 (42), 55 (18), 49 (14), 47 (18), 43 (20), 41 (23), 29 (15), 28 (34).

HRMS (EI, 80 eV): m/z calculated for $[M]^+$: 331.22598, found: 331.22644.

$C_{19}H_{29}N_3O_2 \cdot 1/2 H_2O$ (340.5)	calc.	C 67.03	H 8.80	N 12.34
	found	C 66.68	H 8.29	N 12.29

Synthesis of Methyl 3-[3-(Benzylamino)imidazo[1,2-*a*]pyridin-2-yl]butanoate (95c)

E 20 (IV 25)

Starting amounts:

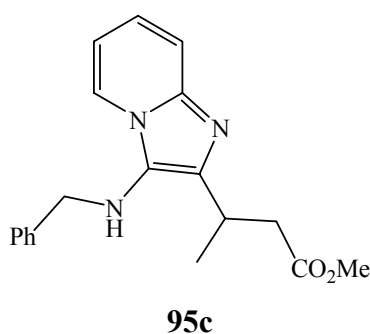
0.202 g	(1.00 mmol)	Siloxycyclopropanecarboxylate 60
0.094 g	(1.00 mmol)	2-Aminopyridine
0.118 g	(1.00 mmol)	Benzylisocyanide
3 ml		MeOH, dry
0.125 g	(2.00 mmol)	Acetic acid 96 %

Procedure according to **U2-AP**

Reaction time: 24 hours

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2, then HPLC (10% *i*-propanol/hexane, 64 ml/min, 80 bar)

Yield: 105 mg (32 %) of **95c** as brownish oil



¹H-NMR (250 MHz, CDCl₃): δ = 1.22 (d, J = 7.0 Hz, 3 H, Me), 2.50–2.76 (m, 2 H, CH₂), 3.10–3.24 (m, 1 H, CH), 3.52 (s, 3 H, OMe), 3.91 (bs, 1 H, NH), 4.04 (d, J = 13.2 Hz, 1 H, CH₂Ph), 4.14 (d, J = 13.2 Hz, 1 H, CH₂Ph), 6.68 (td, J = 6.8, 1.2 Hz, 1 H, 6-H), 7.04 (ddd, J = 9.1, 6.8, 1.2 Hz, 1 H, 7-H), 7.20–7.34 (m, 5 H, Ph), 7.45 (dt, J = 9.1, 1.2 Hz, 1 H, 8-H), 7.95 (dt, J = 6.8, 1.2 Hz, 1 H, 5-H).

¹³C-NMR (62.9 MHz, CDCl₃): δ = 20.3 (q, Me), 27.6 (d, CH), 41.0 (t, CH₂), 51.4 (q, OMe), 52.9 (t, CH₂Ph), 111.1 (d, C-6), 117.0 (d, C-8), 122.3 (d, C-5), 123.0 (d, C-7), 125.1 (s, C-3), 127.4, 128.3, 128.5 (3 d, Ph), 139.5 (s, Ph), 140.1 (s, C-2), 141.4 (s, C-8a), 173.7 (s, C=O).

IR (KBr): ν = 3340 cm⁻¹ (N-H), 2950–2875 (C-H), 1735 (C=O), 1635 (C=N).

MS (EI, 80 eV, 120 °C): m/z (%) = 323 (33, [M]⁺), 233 (15), 232 (100), 205 (11), 200 (20), 173 (12), 145 (12), 91 (18, [Bn]⁺), 78 (41).

HRMS (EI, 80 eV) m/z calculated for [M]⁺: 323.16337, found: 323.16565.

C ₁₉ H ₂₁ N ₃ O ₂ ·1/2 H ₂ O (332.4)	calc.	C 68.65	H 6.67	N 12.64
	found	C 68.62	H 6.19	N 11.71

Synthesis of Methyl 3-[3-(Butylamino)imidazo[1,2-*a*]pyridin-2-yl]butanoate (95d)

Starting amounts:

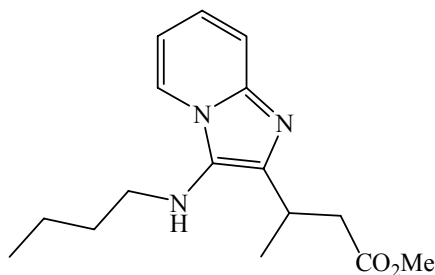
- 0.202 g (1.00 mmol) Siloxycyclopropanecarboxylate **60**
0.094 g (1.00 mmol) 2-Aminopyridine
0.083 g (1.00 mmol) *n*-Butylisocyanide
3 ml MeOH, dry
0.125 g (2.00 mmol) Acetic acid 96 %

Procedure according to **U2-AP**

Reaction time: 19 hours

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2, then HPLC (20% *i*-propanol/hexane, 64 ml/min, 80 bar)

Yield: 123 mg (43 %) of **95d** as brownish oil



95d

¹H-NMR (250 MHz, CDCl₃): δ = 0.89–1.65 (m, 12 H, CH₂, Me), 2.63–3.00 (m, 3 H, CH, CH₂), 3.46–3.60 (m, 1 H, NH), 3.55 (s, 3 H, OMe), 6.73 (td, J = 6.8, 1.2 Hz, 1 H, 6-H), 7.07 (ddd, J = 9.1, 6.8, 1.2 Hz, 1 H, 7-H), 7.47 (dt, J = 9.1, 1.2 Hz, 1 H, 8-H), 8.01 (dt, J = 6.8, 1.2 Hz, 1 H, 5-H).

¹³C-NMR (62.9 MHz, CDCl₃): δ = 13.9 (t, CH₂), 20.2, 20.7 (2 q, Me), 27.8 (d, CH), 32.9, 41.1, 48.8 (3 t, CH₂), 51.4 (q, OMe), 111.2 (d, C-6), 116.9 (d, C-8), 122.4 (d, C-5), 122.8 (d, C-7), 123.2 (s, C-3), 141.3 (s, C-2), 146.0 (s, C-8a), 154.0 (s, C=O).

IR (KBr): ν = 3345 cm⁻¹ (N-H), 2960–2870 (C-H), 1735 (C=O), 1675 (C=N).

MS (EI, 80 eV, 90 °C): m/z (%) = 289 (100, $[M]^+$), 258 (14), 246 (26), 233 (10), 232 (52), 216 (26), 205 (15), 200 (22), 173 (16), 172 (10), 145 (15), 131 (17), 121 (10), 79 (13), 78 (54), 59 (14), 43 (16).

HRMS (EI, 80 eV): m/z calculated for $[M^+, C_{16}H_{23}N_3O_2]$: 289.17902, found: 289.17755.

Synthesis of Methyl 3-[3-(Benzylamino)imidazo[1,2-*a*]pyridin-2-yl]-3-methylbutanoate (**95e**)

Method A

E 22 (IV 24)

Starting amounts:

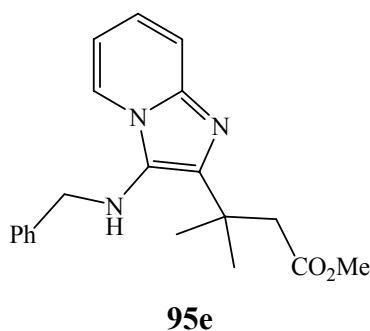
0.216 g (1.00 mmol) Siloxycyclopropanecarboxylate **54**
0.094 g (1.00 mmol) 2-Aminopyridine
0.118 g (1.00 mmol) Benzylisocyanide
3 ml MeOH, dry
0.125 g (2.00 mmol) Acetic acid 96 %

Procedure according to **U2-AP**

Reaction time: 19 hours

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2, then HPLC (15 % *i*-propanol/hexane, 64 ml/min, 80 bar)

Yield: 201 mg (57 %) of **95e** as pale yellow oil



¹H-NMR (250 MHz, CDCl₃): δ = 1.58 (s, 6 H, Me), 2.82 (s, 2 H, CH₂), 3.50 (s, 3 H, OMe), 3.62 (bs, 1 H, NH), 4.13 (s, 2H, CH₂Ph), 6.69 (td, J = 6.8, 1.2 Hz, 1 H, 6-H), 7.06 (ddd, J = 9.0, 6.8, 1.2 Hz, 1 H, 7-H), 7.25–7.49 (m, 6 H, 8-H, Ph), 7.94 (dt, J = 6.8, 1.2 Hz, 1 H, 5-H).

¹³C-NMR (62.9 MHz, CDCl₃): δ = 28.4 (q, Me), 35.3 (s, CMe₂), 46.5 (t, CH₂), 51.1 (q, OMe), 52.9 (t, CH₂Ph), 111.1 (d, C-6), 117.1 (d, C-8), 122.2 (d, C-5), 123.2 (d, C-7), 124.8 (s, C-3), 127.5, 128.0, 128.6 (3 d, Ph), 139.2 (s, Ph), 140.4 (s, C-2), 143.1 (s, C-8a), 172.6 (s, C=O).

IR (KBr): ν = 3375 cm⁻¹ (N-H), 3085–2950 (C-H), 1735 (C=O), 1630 (C=N).

MS (EI, 80 eV, 160 °C): m/z (%) = 337 (32, [M]⁺), 247 (16), 246 (100), 219 (22), 214 (21), 105 (32), 78 (29), 73 (13).

HRMS (EI, 80 eV) m/z calculated for [M]⁺: 337.17902, found: 337.17843.

C ₂₀ H ₂₃ N ₃ O ₂ ·H ₂ O (355.4)	calc.	C 67.59	H 7.09	N 11.82
	found	C 67.69	H 6.22	N 11.95

Method B

E 23 (IV 207)

Starting amounts:

0.216 g	(1.00 mmol)	Siloxycyclopropanecarboxylate 54
0.094 g	(1.00 mmol)	2-Aminopyridine
0.118 g	(1.00 mmol)	Benzylisocyanide
3 ml		MeOH, dry
0.125 g	(2.00 mmol)	Acetic acid 96 %

Procedure: Dry methanol was placed into flame-dried flask under argon atmosphere. Siloxycyclopropanecarboxylate **54**, amine and isocyanide were added to the reaction vessel, followed by addition of acetic acid. The reaction mixture was irradiated in a microwave reactor in 5 cycles. 1 M HCl solution was added to adjust pH 1, the mixture was stirred for 30

min to destroy unreacted isocyanide and evaporated to dryness. The residue was taken up in aqueous NaHCO₃ solution and extracted with ethyl acetate. The combined organic phases were dried with Na₂SO₄ and the solvent was removed under reduced pressure.

Microwave irradiation conditions:

Duration: 60 min

Power: 200 W

Min T: 28 °C

Max T: 30 °C

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 46 mg (14 %) of **95e** as pale yellow oil

Synthesis of Methyl 3-Methyl-3-{3-[(1,1,3,3-tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}butanoate (**64f**) and 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic acid (**96**)

Method A

E 24 (IV 261)

Starting amounts:

0.951 g (4.40 mmol) Siloxycyclopropanecarboxylate **54**
0.376 g (4.00 mmol) 2-Aminopyridine
0.558 g (4.00 mmol) 1,1,3,3-Tetramethylbutylisocyanide
12 ml MeOH, dry
0.500 g (8.00 mmol) Acetic acid 96 %

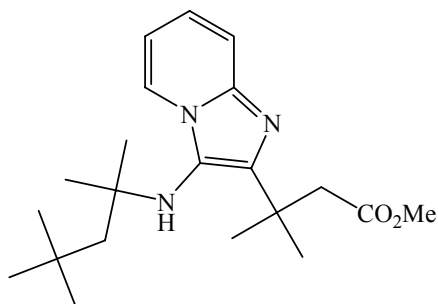
Procedure according to **U2-AP**

Reaction time: 48 hours

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 797 mg (56 %) of **95f** as yellow oil

280 mg (30 %) of **96** as colourless crystals

**95f**

¹H-NMR (250 MHz, CDCl₃): δ = 1.08, 1.22, 1.58 (3 s, 9 H, 6 H, 6 H, Me), 1.69, 2.91 (2 s, 2 H, 2 H, CH₂), 3.11 (s, 1 H, NH), 3.52 (s, 3 H, OMe), 6.63 (td, J = 6.8, 1.2 Hz, 1 H, 6-H), 6.99 (ddd, J = 9.0, 6.8, 1.2 Hz, 1 H, 7-H), 7.38 (dt, J = 9.0, 1.2 Hz, 1 H, 8-H), 8.16 (dt, J = 6.8, 1.2 Hz, 1 H, 5-H).

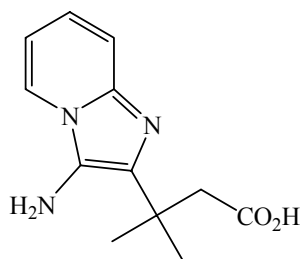
¹³C-NMR (125.8 MHz, CDCl₃): δ = 29.0, 30.3, 31.9 (3 q, Me), 32.0, 35.9 (2 s, CMe₃, CMe₂), 46.6 (t, CH₂), 51.1 (q, OMe), 57.8 (t, CH₂), 58.8 (s, NCMe₂), 110.3 (d, C-6), 116.8 (d, C-8), 122.5 (d, C-5), 123.1 (d, C-7), 123.8 (s, C-3), 140.8 (s, C-2), 144.9 (s, C-8a), 172.6 (s, C=O).

IR (KBr): ν = 3370 cm⁻¹ (N-H), 3075–2870 (C-H), 1735 (C=O), 1630 (C=N).

MS (EI, 80 eV, 80°C): m/z (%) = 359 (66, [M]⁺), 328 (11), 248 (18), 247 (86), 246 (100), 219 (29), 215 (13), 214 (51), 188 (17), 174 (44), 105 (17).

HRMS (EI, 80 eV): m/z calculated for [M]⁺: 359.25726, found: 359.25544.

C ₂₁ H ₃₃ N ₃ O ₂ (359.5)	calc.	C 70.16	H 9.25	N 11.69
	found	C 69.90	H 9.14	N 11.70

**96**

Melting point: 250–251°C

¹H-NMR (500 MHz, CD₃OD): δ = 1.47 (s, 6 H, Me), 2.78 (s, 2 H, CH₂), 6.88 (td, J = 6.8, 1.2 Hz, 1 H, 6-H), 7.13 (ddd, J = 9.2, 6.8, 1.2 Hz, 1 H, 7-H), 7.44 (dt, J = 9.2, 1.2 Hz, 1 H, 8-H), 8.06 (dt, J = 6.8, 1.2 Hz, 1 H, 5-H).

¹³C-NMR (125.8 MHz, CD₃OD): δ = 27.2 (q, Me), 33.1 (s, CMe₂), 48.0 (t, CH₂), 113.8 (d, C-6), 117.5 (d, C-8), 121.3 (d, C-5), 122.5 (d, C-7), 123.9 (d, C-3), 139.3 (s, C-2), 142.1 (s, C-9), 172.4 (s, C=O).

IR (KBr): ν = 3335–2865 cm⁻¹ (OH, NH, CH), 1680 (C=O), 1570 (C=N), 1235 (C-O).

MS (EI, 80 eV, 160 °C): m/z (%) = 215 (87, [M - H₂O]⁺), 201 (29), 200 (100), 173 (13), 172 (11), 158 (12), 145 (20), 79 (19), 78 (57), 52 (10), 51 (17), 41 (12), 39 (12), 28 (16), 27 (10).

HRMS (EI, 80 eV) m/z calculated for [M - H₂O]⁺: 215.10587, found: 215.10633.

C ₁₂ H ₁₅ N ₃ O ₂ (233.3)	calc.	C 61.73	H 6.48	N 18.01
	found	C 61.49	H 5.28	N 17.00

Method B

E 25 (IV 301)

Starting amounts:

0.951 g	(4.40 mmol)	Siloxycyclopropanecarboxylate 54
0.376 g	(4.00 mmol)	2-Aminopyridine
0.558 g	(4.00 mmol)	1,1,3,3-Tetramethylbutylisocyanide
12 ml		MeOH, dry
0.500 g	(8.00 mmol)	Acetic acid 96 %

Procedure according to **U2-AP**

Reaction time: 72 hours

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 559 mg (60 %) of **96** as colourless crystals

Synthesis of Methyl 3-{3-[(4-Methoxyphenyl)amino]imidazo[1,2-*a*]pyridin-2-yl}-3-methylbutanoate (**95g**)

Method A

E 26 (IV 126)

Starting amounts:

0.238 g (1.10 mmol) Siloxycyclopropanecarboxylate **54**

0.094 g (1.00 mmol) 2-Aminopyridine

0.133 g (1.00 mmol) *p*-Methoxyphenylisocyanide

3 ml MeOH, dry

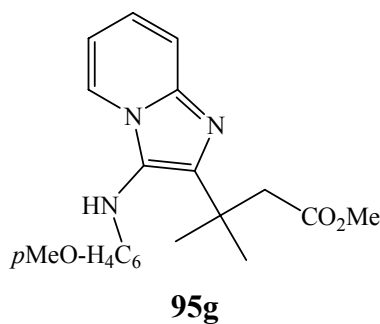
0.125 g (2.00 mmol) Acetic acid 96 %

Procedure according to **U2-AP**

Reaction time: 20 hours

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 152 mg (43 %) of **95g** as brownish crystals



Melting point: 140–143 °C

¹H-NMR (250 MHz, CDCl₃): δ = 1.50 (s, 6 H, Me), 2.82 (s, 2 H, CH₂), 3.55, 3.72 (2 s, 3 H, 3 H, OMe), 5.79 (s, 1 H, NH), 6.20–6.26 (m, 2 H, Ar), 6.50 (td, J = 6.8, 1.2 Hz, 1 H, 6-H), 6.54–6.60 (m, 2 H, Ar), 6.94 (ddd, J = 9.1, 6.8, 1.2 Hz, 1 H, 7-H), 7.34 (dt, J = 9.1, 1.2 Hz, 1 H, 8-H), 7.58 (dt, J = 6.8, 1.2 Hz, 1 H, 5-H).

¹³C-NMR (62.9 MHz, CDCl₃): δ = 28.3 (q, Me), 35.3 (s, CMe₂), 46.0 (t, CH₂), 51.1 (q, OMe), 55.6 (q, *p*-OMe), 111.4 (d, C-6), 114.0 (d, C-8), 115.1 (d, C-5), 117.2 (d, C-7), 118.6 (s, C-3), 122.6, 124.0 (2 d, Ar), 139.2 (s, Ar), 141.4 (s, C-2), 146.3 (s, C-8a), 153.1 (s, Ar), 172.9 (s, C=O).

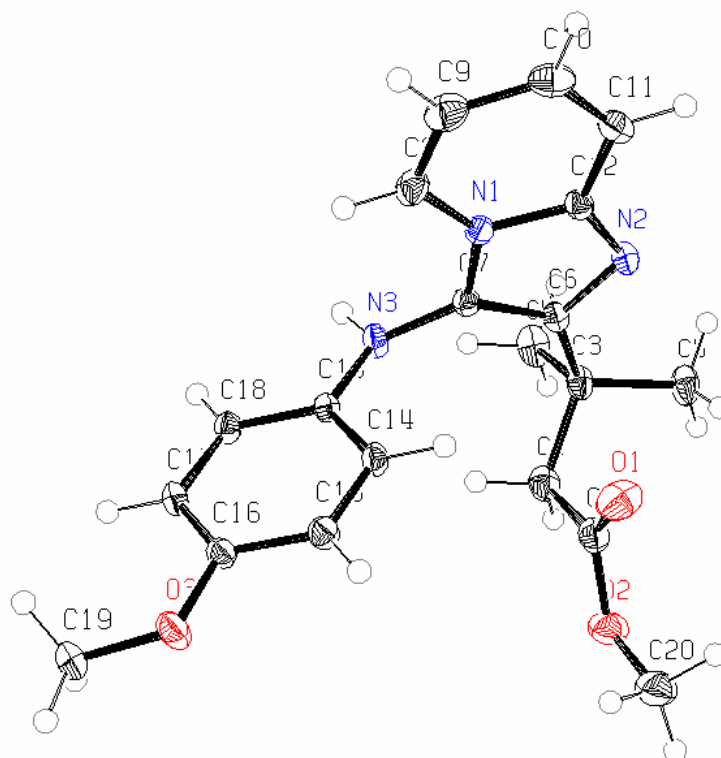
IR (KBr): ν = 3270 cm⁻¹ (N-H), 3105–2825 (C-H), 1730 (C=O), 1675 (C=N).

MS (EI, 80 eV, 120 °C): m/z (%) = 354 (100, [M]⁺), 294 (30), 282 (13), 281 (38), 151 (11), 147 (25), 112 (15), 108 (10), 105 (16), 97 (10), 95 (12), 94 (42), 91 (13), 86 (21), 85 (16), 84 (42), 83 (17), 82 (11), 79 (15), 78 (28), 73 (21), 71 (23), 70 (20), 69 (32), 67 (15), 60 (22), 59 (11), 58 (13), 57 (46), 56 (19), 55 (35), 49 (10), 45 (37), 44 (37), 43 (71), 42 (14), 41 (38), 39 (19), 32 (18).

C ₂₀ H ₂₃ N ₃ O ₃ (353.4)	calc.	C 67.97	H 6.56	N 11.89
	found	C 67.83	H 6.47	N 11.44

Crystal data and structure refinement for **95j**:

Crystals of **95j** for X-ray analysis have been obtained after keeping the substance at low temperature (in refrigerator) for several months.



Empirical formula	C ₂₀ H ₂₃ N ₃ O ₃	
Formula weight	353.41	
Temperature	173(2) K	
Wavelength	0.71073 Å	
Crystal system	monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.870(4) Å	α = 90°.
	b = 10.817(4) Å	β = 98.166(8)°.
	c = 17.218(7) Å	γ = 90°.
Volume	1819.6(13) Å ³	
Z	4	
Density (calculated)	1.290 Mg/m ³	
Absorption coefficient	0.088 mm ⁻¹	
F(000)	752	
Crystal size	.5 x .2 x .1 mm ³	
Theta range for data collection	2.08 to 30.55°.	
Index ranges	-12 ≤ h ≤ 14, -15 ≤ k ≤ 14, -22 ≤ l ≤ 24	
Reflections collected	13376	
Independent reflections	5119 [R(int) = 0.0296]	

Completeness to theta = 30.55°	91.9 %
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	5119 / 0 / 244
Goodness-of-fit on F ²	1.153
Final R indices [I>2sigma(I)]	R1 = 0.0526, wR2 = 0.1346
R indices (all data)	R1 = 0.0673, wR2 = 0.1400
Extinction coefficient	0.025(2)
Largest diff. peak and hole	0.371 and -0.257 e.Å ⁻³

Table 16. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **95g**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
N(3)	6086(1)	1874(1)	8198(1)	19(1)
N(2)	3785(1)	4027(1)	7032(1)	18(1)
N(1)	4068(1)	3164(1)	8232(1)	16(1)
O(3)	10278(1)	3244(1)	10582(1)	24(1)
O(1)	6951(1)	5322(1)	7358(1)	35(1)
O(2)	8853(1)	5024(1)	6806(1)	29(1)
C(19)	11157(2)	2330(2)	10989(1)	26(1)
C(16)	9254(2)	2833(2)	10007(1)	17(1)
C(17)	8929(2)	1599(1)	9849(1)	19(1)
C(18)	7870(2)	1289(1)	9253(1)	17(1)
C(13)	7121(2)	2207(1)	8810(1)	16(1)
C(14)	7452(2)	3447(1)	8978(1)	18(1)
C(15)	8509(2)	3754(1)	9567(1)	19(1)
C(7)	5121(2)	2723(1)	7847(1)	16(1)
C(8)	3791(2)	2970(2)	8982(1)	23(1)
C(9)	2684(2)	3540(2)	9213(1)	29(1)
C(10)	1820(2)	4307(2)	8690(1)	28(1)
C(11)	2110(2)	4502(2)	7947(1)	23(1)
C(12)	3278(2)	3941(1)	7709(1)	17(1)
C(6)	4931(2)	3283(1)	7121(1)	16(1)
C(3)	5779(2)	3122(2)	6462(1)	20(1)
C(4)	5593(2)	1792(2)	6147(1)	27(1)
C(5)	5313(2)	4021(2)	5783(1)	26(1)
C(2)	7318(2)	3344(2)	6760(1)	23(1)
C(1)	7645(2)	4659(2)	7013(1)	24(1)
C(20)	9263(2)	6269(2)	7044(1)	35(1)

Method B

E 27 (IV 202)

Starting amounts:

0.238 g	(1.10 mmol)	Siloxycyclopropanecarboxylate 54
0.094 g	(1.00 mmol)	2-Aminopyridine
0.133 g	(1.00 mmol)	<i>p</i> -Methoxyphenylisocyanide
3 ml		MeOH, dry
0.125 g	(2.00 mmol)	Acetic acid 96 %

Procedure: Dry methanol was placed into a flame-dried flask under an argon atmosphere. Siloxycyclopropanecarboxylate **54**, amine and isocyanide were added to the reaction vessel, followed by addition of acetic acid. The reaction mixture was irradiated in a microwave reactor in 5 cycles. 1 M HCl solution was added to adjust pH 1; the mixture was stirred for 30 min to destroy unreacted isocyanide and evaporated to dryness. The residue was taken up in aqueous NaHCO₃ solution and extracted with ethyl acetate. The combined organic phases were dried with Na₂SO₄ and the solvent was removed under reduced pressure.

Microwave irradiation conditions:

Duration: 60 min
Power: 200 W
Min T: 28 °C
Max T: 30 °C

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 218 mg (62 %) of **95g** as brownish crystals.**Synthesis of Methyl 3-[3-(Benzylamino)imidazo[1,2-*a*]pyridin-2-yl]-2,3-dimethylbutanoate (**95h**)**

E 28 (IV 164)

Starting amounts:

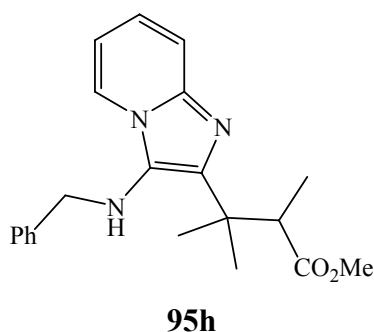
0.277 g (1.20 mmol) Siloxycyclopropanecarboxylate **56**
0.094 g (1.00 mmol) 2-Aminopyridine
0.118 g (1.00 mmol) Benzylisocyanide
3 ml MeOH, dry
0.125 g (2.00 mmol) Acetic acid 96 %

Procedure according to **U2-AP**

Reaction time: 17 hours

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 140 mg (40 %) of **95h** as pale yellow oil



¹H-NMR (250 MHz, CDCl₃): δ = 1.06 (d, J = 7.2 Hz, 3 H, Me), 1.54 (s, 6 H, Me), 3.17 (q, J = 7.2 Hz, 1 H, CH), 3.44 (t, J = 6.4 Hz, 1 H, NH), 3.50 (s, 3 H, OMe), 4.07 (d, J = 6.4 Hz, 2H, CH₂Ph), 6.66 (td, J = 6.8, 1.1 Hz, 1 H, 6-H), 7.04 (ddd, J = 9.0, 6.8, 1.1 Hz, 1 H, 7-H), 7.24–7.55 (m, 6 H, 8-H, Ph), 7.91 (dt, J = 6.8, 1.1 Hz, 1 H, 5-H).

¹³C-NMR (62.9 MHz, CDCl₃): δ = 13.1, 24.0, 26.0 (3 q, Me), 38.5 (s, CMe₂), 48.5 (d, CH), 51.0 (q, OMe), 52.8 (t, CH₂Ph), 111.2 (d, C-6), 117.0 (d, C-8), 122.1 (d, C-5), 123.3 (d, C-7), 125.3 (s, C-3), 127.5, 127.9, 128.6 (3 d, Ph), 139.0 (s, Ph), 140.2 (s, C-2), 142.3 (s, C-8a), 176.2 (s, C=O).

IR (KBr): ν = 3375 cm⁻¹ (N-H), 3085–2950 (C-H), 1735 (C=O), 1630 (C=N).

MS (EI, 80 eV, 120 °C): m/z (%) = 351 (34, $[M]^+$), 264 (14), 261 (20), 260 (100), 233 (16), 229 (12), 228 (66), 201 (10), 174 (16), 176 (15), 158 (14), 121 (21) 105 (19), 91 (10, $[Bn]^+$), 78 (13).

HRMS (EI, 80 eV) m/z calculated for $[M]^+$: 351.19467, found: 351.19633.

7.3.1 Cyclization reactions

Cyclization reaction of **95e** to compound **100e**

E 29 (IV 91)

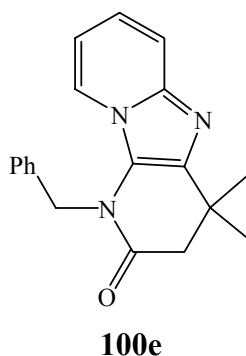
Starting amounts:

0.060 g	(0.178 mmol) Methyl 3-[3-(Benzylamino)imidazo[1,2- <i>a</i>]pyridin-2-yl]-3-methylbutanoate (95e)
1 mg	(0.02 mmol) Sodium cyanide
2 ml	MeOH, dry

Procedure: Dry methanol was placed into a flame-dried flask under an argon atmosphere. Methyl 3-[3-(benzylamino)imidazo[1,2-*a*]pyridin-2-yl]-3-methylbutanoate (**95e**) was added to the reaction vessel, followed by addition of sodium cyanide. The reaction mixture was heated ($t_{\text{bath}} = 85\text{ °C}$) for 43 hours, and then the solvent was evaporated to dryness. Ethyl acetate and water were added and the layers were separated. The aqueous layer was extracted with ethyl acetate, the combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure.

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1

Yield: 50 mg (92 %) of **100e** as colourless crystals

**100e**

Melting point: 138–140 °C

¹H-NMR (250 MHz, CDCl₃): δ = 1.38 (s, 6 H, Me), 2.74 (s, 2 H, CH₂), 5.23 (s, 2 H, CH₂Ph), 6.64 (td, J = 6.9, 1.2 Hz, 1 H, 6-H), 7.01 (ddd, J = 9.1, 6.9, 1.2 Hz, 1 H, 7-H), 7.23–7.37 (m, 5 H, Ph), 7.55 (dt, J = 9.1, 1.2 Hz, 1 H, 8-H), 7.77 (dt, J = 6.9, 1.2 Hz, 1 H, 5-H).

¹³C-NMR (62.9 MHz, CDCl₃): δ = 26.3 (q, Me), 31.5 (s, CMe₂), 46.5, 48.4 (2 t, CH₂), 112.6 (d, C-6), 118.2 (d, C-8), 121.6 (d, C-5), 121.8 (d, C-7), 122.0 (s, C-3), 126.7, 127.7, 128.9 (3 d, Ph), 136.6 (s, Ph), 138.6 (s, C-2), 141.4 (s, C-8a), 170.9 (s, C=O).

IR (KBr): ν = 3065–2865 cm⁻¹ (C-H), 1680 (C=O), 1630 (C=N).

MS (EI, 80 eV, 190 °C): m/z (%) = 305 (32, [M]⁺), 215 (14), 214 (100, [M - Bn]⁺), 91 (13, [Bn]⁺), 78 (18).

HRMS (EI, 80 eV) m/z calculated for [M⁺, C₁₉H₁₉N₃O]: 305.15280, found: 305.15355.

Cyclization reaction of 95g to compound 100g

E 30 (IV 186)

Starting amounts:

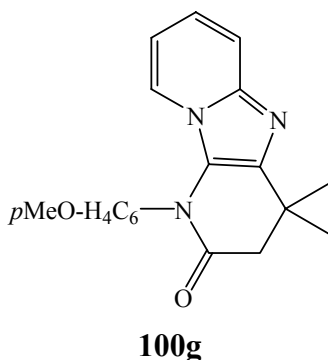
- | | |
|---------|---|
| 0.134 g | (0.38 mmol) Methyl 3-{3-[(4-methoxyphenyl)amino]imidazo[1,2- <i>a</i>]pyridin-2-yl}-3-methylbutanoate (95g) |
| 2 mg | (0.04 mmol) Sodium cyanide |
| 4 ml | MeOH, dry |

Procedure: Dry methanol was placed into a flame-dried flask under an argon atmosphere. Methyl 3-{3-[(4-methoxyphenyl)amino]imidazo[1,2-*a*]pyridin-2-yl}-3-methylbutanoate (**95g**) was added to the reaction vessel, followed by addition of sodium cyanide. The reaction mixture was heated ($t_{\text{bath}} = 85^{\circ}\text{C}$) for 48 hours, and then the solvent was evaporated to dryness. Ethyl acetate and water were added and the layers separated. The aqueous layer was extracted with ethyl acetate, the combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 37 mg (30 %) of **100g** as brownish solid

55 mg (40 %) of **95g** as brownish solid was recovered



Melting point: 160–162 °C

$^1\text{H-NMR}$ (250 MHz, CDCl_3): $\delta = 1.48$ (s, 6 H, Me), 2.78 (s, 2 H, CH_2), 3.83 (s, 3 H, OMe), 6.47 (td, $J = 6.9, 1.2$ Hz, 1 H, 6-H), 6.79 (ddd, $J = 9.1, 6.9, 1.2$ Hz, 1 H, 7-H), 6.94–7.01 (m, 3 H, 8-H, Ar), 7.13–7.19 (m, 2 H, Ar), 7.55 (dt, $J = 6.9, 1.2$ Hz, 1 H, 5-H).

$^{13}\text{C-NMR}$ (125.8 MHz, CDCl_3): $\delta = 26.6$ (q, Me), 31.8 (s, CMe_2), 48.9 (t, CH_2), 55.5 (q, OMe), 112.0 (d, C-6), 114.8 (d, C-8), 117.8 (d, C-5), 120.9 (s, C-3), 121.7 (d, C-7), 121.9, 127.7 (2 d, Ar), 128.6 (s, Ar), 138.8 (s, C-2), 141.5 (s, C-8a), 158.9 (s, Ar), 170.0 (s, C=O).

IR (KBr): $\nu = 3445\text{--}2855$ cm^{-1} (C-H), 1690 (C=O), 1510 (C=N).

MS (EI, 80 eV, 110 °C): m/z (%) = 321 (100, $[\text{M}]^+$), 307 (12), 306 (54), 261 (11), 233 (24), 156 (11), 149 (25), 145 (12), 135 (11), 123 (10), 121 (13), 111 (17), 99 (12), 97 (19), 95 (15),

94 (27), 85 (18), 83 (27), 81 (12), 79 (10), 78 (21), 71 (23), 70 (12), 69 (31), 67 (24), 57 (49), 56 (20), 55 (36), 45 (12), 43 (49), 42 (11), 41 (39), 39 (14), 32 (12), 31 (13), 29 (29), 28 (58), 27 (15).

HRMS (EI, 80 eV) m/z calculated for $[M^+, C_{19}H_{19}N_3O_2]$: 321.14774, found: 321.14844.

Cyclization reaction of **95h** to compound **100h**

E 31 (IVMK5)

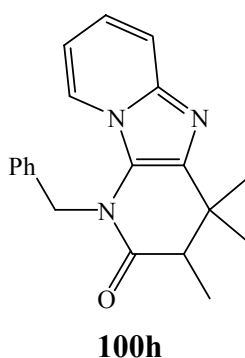
Starting amounts:

0.414 g (1.12 mmol) Methyl 3-[3-(Benzylamino)imidazo[1,2-*a*]pyridin-2-yl]-2,3-dimethylbutanoate (**95h**)
6 mg (0.12 mmol) Sodium cyanide
14 ml MeOH, dry

Procedure: Dry methanol was placed into a flame-dried flask under an argon atmosphere. Methyl 3-[3-(Benzylamino)imidazo[1,2-*a*]pyridin-2-yl]-2,3-dimethylbutanoate (**95h**) was added to the reaction vessel, followed by addition of sodium cyanide. The reaction mixture was heated ($t_{\text{bath}} = 85\text{ }^\circ\text{C}$) for 48 hours, and then the solvent was evaporated to dryness. Ethyl acetate and water were added and the layers separated. The aqueous layer was extracted with ethyl acetate, the combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure.

Purification: Column chromatography on activated alox with hexane/ethyl acetate 1:1

Yield: 350 mg (98 %) of **100h** as colourless crystals



Melting point: 114–115 °C

¹H-NMR (500 MHz, CDCl₃): δ = 1.11 (s, 3 H, Me), 1.19 (d, J = 7.1 Hz, 3 H, Me), 1.42 (s, 3 H, Me), 2.66 (q, J = 7.1 Hz, 1 H, 10-H), 5.16 (dd, J = 16.3 Hz, 2 H, CH₂), 6.62 (td, J = 6.9, 1.2 Hz, 1 H, 6-H), 6.98 (ddd, J = 9.1, 6.9, 1.2 Hz, 1 H, 7-H), 7.19–7.33 (m, 5 H, Ph), 7.54 (dt, J = 9.1, 1.2 Hz, 1 H, 8-H), 7.72 (dt, J = 6.9, 1.2 Hz, 1 H, 5-H).

¹³C-NMR (125.8 MHz, CDCl₃): δ = 10.0, 21.3, 25.3 (3 q, Me), 34.3 (s, CMe₂), 46.6 (t, CH₂), 48.8 (d, CH), 112.5 (d, C-6), 118.1 (d, C-8), 121.3 (d, C-5), 121.5 (d, C-7), 121.7 (s, C-3), 126.6, 127.6, 128.8 (3 d, Ph), 136.7 (s, Ph), 139.0 (s, C-2), 141.2 (s, C-8a), 173.9 (s, C=O).

IR (KBr): ν = 3085–2870 cm⁻¹ (C-H), 1680 (C=O), 1635 (C=N).

MS (EI, 80 eV, 60 °C): m/z (%) = 319 (53, [M]⁺), 258 (17), 229 (17), 228 (100, [M - Bn]⁺), 121 (30), 108 (22), 106 (17), 94 (25), 91 (38, [Bn]⁺), 86 (37), 84 (64), 79 (10), 78 (33), 70 (37), 69 (15), 67 (17), 57 (10), 55 (23), 51 (11), 49 (11), 47 (16), 45 (10), 44 (11), 43 (21), 42 (11), 41 (24), 39 (13), 32 (17), 29 (12), 28 (96), 27 (13).

HRMS (EI, 80 eV) m/z calculated for [M]⁺, C₂₀H₂₁N₃O]: 319.16846, found: 319.16655.

7.3.2 Dealkylation and hydrolysis reactions

Synthesis of Methyl 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)propanoate (**101**)

E 32 (IV 315)

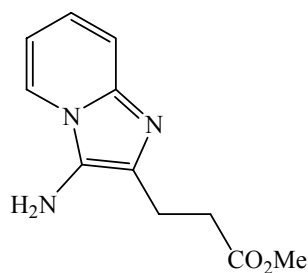
Starting amounts:

0.643 g (1.94 mmol) Methyl 3-{3-[(1,1,3,3-tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}propanoate (**95b**)
5 ml TFA/CH₂Cl₂ 1:1

Procedure: Methyl 3-{3-[(1,1,3,3-tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}propanoate (**95b**) was dissolved in TFA/CH₂Cl₂ 1:1 solution and stirred for 2 hours at room temperature. The reaction mixture was loaded on a Dowex cation exchange resin, washed with methanol until it was acid-free and then eluted with saturated methanolic ammonia. The solvent was removed under reduced pressure.

Purification: Column chromatography on silica gel with methanol/dichloromethane 1:19

Yield: 399 mg (94 %) of **101** as yellowish oil.



101

¹H-NMR (500 MHz, CDCl₃): δ = 2.78 (t, *J* = 6.7 Hz, 2 H, CH₂), 3.02 (t, *J* = 6.7 Hz, 2 H, CH₂), 3.52 (s, 3 H, OMe), 6.05 (bs, 2 H, NH₂), 6.76 (t, *J* = 6.8, 1 H, 6-H), 7.03–7.19 (m, 1 H, 7-H), 7.42 (d, *J* = 9.1 Hz, 1 H, 8-H), 8.00 (d, *J* = 6.8 Hz, 1 H, 5-H).

^{13}C -NMR (125.8 MHz, CDCl_3): δ = 21.6, 33.2 (2 t, CH_2), 51.6 (q, OMe), 111.6 (d, C-6), 116.7 (d, C-8), 122.1 (d, C-5), 123.3 (d, C-7), 123.4 (s, C-3), 132.7 (s, C-2), 140.2 (s, C-8a), 174.1 (s, C=O).

IR (KBr): ν = 3320–3180 cm^{-1} (N-H), 2950–2850 (C-H), 1730 (C=O), 1670 (C=N).

MS (EI, 80 eV, 100 °C): m/z (%) = 219 (58, $[\text{M}]^+$), 188 (16), 161 (14), 160 (100), 159 (19), 146 (52), 133 (14), 121 (16), 119 (25), 115 (14), 91 (10), 80 (24), 79 (82), 67 (12), 59 (12), 55 (15), 51 (17), 28 (16).

HRMS (EI, 80 eV): m/z calculated for $[\text{M}^+, \text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_2]$: 219.10078, found: 219.10155.

Synthesis of 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic acid (**96**)

E 33 (IV 266)

Starting amounts:

0.861 g (2.40 mmol) Methyl 3-Methyl-3-{3-[(1,1,3,3-tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}butanoate (**95f**)
5 ml TFA/ CH_2Cl_2 1:1

Procedure: Methyl 3-Methyl-3-{3-[(1,1,3,3-tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}butanoate (**95f**) was dissolved in TFA/ CH_2Cl_2 1:1 solution and stirred for 2 hours at room temperature. The reaction mixture was loaded on a Dowex cation exchange resin, washed with methanol until it was acid-free and then eluted with methanolic ammonia. The solvent was removed under reduced pressure.

Purification: Column chromatography on silica gel with methanol/dichloromethane 1:19

Yield: 450 mg (80 %) of **96** as colourless crystals - for analytical data see E22 (IV261)

Synthesis of Methyl 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoate (102) and 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic acid (96)

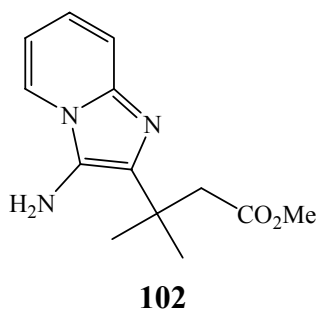
E 34 (IV 206)

Starting amounts:

0.116 g (0.32 mmol) Methyl 3-Methyl-3-{3-[(1,1,3,3-tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}butanoate (**95f**)
2 ml TFA/CH₂Cl₂ 1:1

Procedure: Methyl 3-Methyl-3-{3-[(1,1,3,3-tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}butanoate (**95f**) was dissolved in TFA/CH₂Cl₂ 1:1 solution and stirred for 5 min at room temperature. The reaction mixture was loaded on a Dowex cation exchange resin, washed with methanol until it was acid-free and then eluted with methanolic ammonia. The solvent was removed under reduced pressure.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 20 mg (25 %) of **102** as yellow oil37 mg (50 %) of **96** as colourless crystals – for analytical data see E22 (IV261)

¹H-NMR (500 MHz, CDCl₃): δ = 1.35 (s, 6 H, Me), 2.54 (s, 2 H, CH₂), 3.91 (s, 3 H, OMe), 6.75 (td, *J* = 6.7, 1.2 Hz, 1 H, 6-H), 7.02 (ddd, *J* = 9.0, 6.7, 1.2 Hz, 1 H, 7-H), 7.49 (dt, *J* = 9.0, 1.2 Hz, 1 H, 8-H), 8.09 (dt, *J* = 6.7, 1.2 Hz, 1 H, 5-H); the NH₂ signal could not be detected.

^{13}C -NMR (125.8 MHz, CDCl_3): δ = 27.0 (q, Me), 32.2 (s, CMe_2), 42.8 (t, CH_2), 53.7 (q, OMe), 111.8 (d, C-6), 117.1 (d, C-8), 121.5 (d, C-5), 122.4 (d, C-7), 127.5 (s, C-3), 135.8 (s, C-2), 141.9 (s, C-8a), 165.9 (s, C=O).

IR (KBr): ν = 3380–3085 cm^{-1} (O-H, N-H), 2950–2875 (C-H), 1720 (C=O), 1610 (C=N).

MS (EI, 80 eV, 50 °C): m/z (%) = 229 (100, $[\text{M} - \text{NH}_4]^+$), 215 (14), 214 (95), 200 (15), 199 (14), 111 (10), 109 (10), 108 (11), 107 (15), 99 (13), 97 (14), 95 (15), 94 (11), 91 (25), 85 (21), 84 (14), 83 (21), 82 (13), 81 (14), 79 (17), 78 (21), 73 (20), 71 (30), 70 (18), 69 (28), 67 (15), 60 (33), 59 (11), 58 (25), 57 (37), 56 (28), 55 (40), 51 (10), 45 (25), 44 (14), 43 (74), 42 (17), 41 (46), 39 (22), 29 (31), 28 (64), 27 (27).

HRMS (EI, 80 eV) m/z calculated for $[\text{M}^+ - \text{NH}_4, \text{C}_{13}\text{H}_{13}\text{N}_2\text{O}_2]$: 229.09770, found: 229.09822.

Synthesis of Methyl 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)propanoate (**101**) and compound (**103**)

E 35 (IV 354)

Starting amounts:

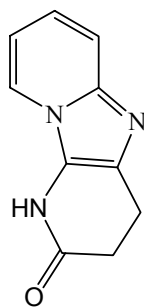
0.420 g (1.27 mmol) Methyl 3-{3-[(1,1,3,3-Tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}propanoate (**95b**)
6 ml TFA/ CH_2Cl_2 1:1

Procedure: Methyl 3-{3-[(1,1,3,3-Tetramethylbutyl)amino]imidazo[1,2-*a*]pyridin-2-yl}propanoate (**95b**) was dissolved in TFA/ CH_2Cl_2 1:1 solution and stirred for 2 h at room temperature. The reaction mixture was loaded on a Dowex cation exchange resin, washed with methanol until it was acid-free and then eluted with methanolic ammonia. The solvent was removed under reduced pressure.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 118 mg (42 %) of **101** as yellowish oil - for analytical data see E31 (IV315)

47 mg (20 %) of **103** as brownish solid

**103**

Melting range: 278–282 °C

¹H-NMR (500 MHz, CD₃OD): δ = 2.83 (t, J = 7.7 Hz, 2 H, CH₂), 3.07 (t, J = 7.7 Hz, 2 H, CH₂), 6.91 (td, J = 6.9, 1.1 Hz, 1 H, 6-H), 7.16 (ddd, J = 9.1, 6.9, 1.1 Hz, 1 H, 7-H), 7.44 (dt, J = 9.1, 1.1 Hz, 1 H, 8-H), 8.08 (dt, J = 6.9, 1.1 Hz, 1 H, 5-H).

¹³C-NMR (125.8 MHz, CD₃OD): δ = 21.5, 33.1 (2 t, CH₂), 114.1 (d, C-6), 117.7 (d, C-8), 122.6 (d, C-5), 124.4 (d, C-7), 129.8 (s, C-3), 135.9 (s, C-2), 142.4 (s, C-8a), 172.8 (s, C=O).

IR (KBr): ν = 3440 cm⁻¹ (N-H), 3100–2860 (C-H), 1675 (C=O), 1625 (C=N).

MS (EI, 80 eV, 140 °C): m/z (%) = 187 (62, [M]⁺), 160 (14), 159 (41), 145 (16), 144 (29), 132 (20), 131 (18), 118 (19), 94 (15), 79 (43), 78 (100), 67 (20), 52 (19), 51 (29), 44 (14), 39 (14), 28 (38), 27 (12).

HRMS (EI, 80 eV) m/z calculated for [M⁺, C₁₀H₉N₃O]: 187.0745, found: 187.0744.

Synthesis of 3-[3-(Benzylamino)imidazo[1,2-*a*]pyridin-2-yl]-3-methylbutanoic acid (104)

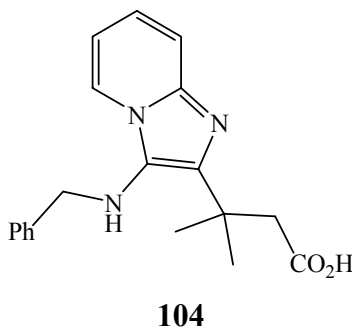
Starting amounts:

0.109 g	(0.32 mmol)	Methyl 3-[3-(Benzylamino)imidazo[1,2- <i>a</i>]pyridin-2-yl]-3-methylbutanoate (95e)
0.041 g	(0.96 mmol)	LiOH·H ₂ O
1 ml		H ₂ O
1 ml		MeOH
3 ml		THF

Procedure: Methyl 3-[3-(benzylamino)imidazo[1,2-*a*]pyridin-2-yl]-3-methylbutanoate (**95e**) was dissolved in a mixture of methanol and tetrahydrofuran, a solution of LiOH in water was added, and the resulting mixture was stirred 22 hours at room temperature. 2 M HCl was added to adjust pH 7. Diethyl ether was added and the layers were separated. The aqueous layer was extracted with diethyl ether, the combined organic phases were dried with MgSO₄ and the solvent was evaporated.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 80 mg (77 %) of **104** as pale yellow solid



Melting range: 111–115 °C

¹H-NMR (250 MHz, CDCl₃): δ = 1.38 (s, 6 H, Me), 2.74 (s, 2 H, CH₂), 5.23 (s, 2 H, CH₂Ph), 6.65 (td, *J* = 6.9, 1.2 Hz, 1 H, 6-H), 7.01 (ddd, *J* = 9.1, 6.9, 1.2 Hz, 1 H, 7-H), 7.24–7.40 (m, 5 H, Ph), 7.56 (dt, *J* = 9.1, 1.2 Hz, 1 H, 8-H), 7.76 (dt, *J* = 6.9, 1.2 Hz, 1 H, 5-H); the NH signal could not be detected.

^{13}C -NMR (62.9 MHz, CDCl_3): δ = 26.4 (q, Me), 31.6 (s, CMe_2), 46.6 (t, CH_2), 48.5 (t, CH_2Ph), 112.8 (d, C-6), 118.2 (d, C-8), 121.8 (d, C-5), 121.9 (d, C-7), 122.1 (s, C-3), 126.8, 127.8, 129.0 (3 d, Ph), 136.7 (s, Ph), 138.6 (s, C-2), 141.5 (s, C-8a), 171.0 (s, C=O).

IR (KBr): ν = 3230–3030 cm^{-1} (O-H, N-H), 2960–2870 (C-H), 1680 (C=O), 1235 (C-O).

MS (EI, 80 eV, 190 °C): m/z (%) = 323 (31, $[\text{M}]^+$), 305 (32), 233 (16), 232 (100, $[\text{M} - \text{Bn}]^+$), 215 (14), 214 (94), 205 (42), 121 (31), 105 (17), 91 (39, $[\text{Bn}]^+$), 83 (11), 79 (14), 78 (59), 41 (11), 28 (12).

HRMS (EI, 80 eV) m/z calculated for $[\text{M}]^+$: 323.16337, found: 323.16632.

$\text{C}_{19}\text{H}_{21}\text{N}_3\text{O}_2$ (323.4)	calc.	C 70.57	H 6.55	N 12.99
	found	C 69.87	H 6.63	N 13.52

7.3.3 Reaction with RuO₄

Synthesis of 1-Benzyl-4,4-dimethylpiperidine-2,3,6-trione (**105**)

E 37 (IV 93)

Starting amounts:

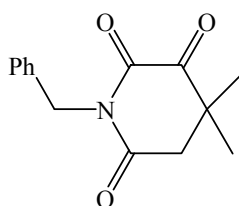
0.137 g	(0.422 mmol)	3-[3-(Benzylamino)imidazo[1,2- <i>a</i>]pyridin-2-yl]-3-methylbutanoic acid (104)
0.360 g	(1.68 mmol)	NaIO ₄
1 mg	(0.008 mmol)	RuO ₂ ·H ₂ O
1.0 ml		MeCN
1.0 ml		CH ₂ Cl ₂
1.5 ml		H ₂ O

Procedure: 3-[3-(Benzylamino)imidazo[1,2-*a*]pyridin-2-yl]-3-methylbutanoic acid (**104**) was dissolved in a MeCN/CH₂Cl₂/H₂O mixture, then NaIO₄ and RuO₂·H₂O were added. The reaction mixture was stirred for 2 hours at room temperature. 5 ml Water and 5 ml dichloromethane were added and the layers were separated. The aqueous layer was extracted with dichloromethane, the combined organic layers were dried with Na₂SO₄ and the solvent was removed under reduced pressure. The residue was dissolved in diethyl ether and filtered through a pad of celite and the solvent was evaporated to dryness.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 37 mg (36 %) of **105** as colourless solid

21 mg (15 %) of **104** was recovered as pale yellow solid



105

Melting point: >300 °C

¹H-NMR (250 MHz, CDCl₃): δ = 1.24 (s, 6 H, Me), 2.87 (s, 2 H, CH₂), 4.99 (s, 2 H, CH₂Ph), 7.18–7.50 (m, 5 H, Ph).

¹³C-NMR (62.9 MHz, CDCl₃): δ = 23.2 (q, Me), 42.8 (s, C-4), 44.0, 44.8 (2 t, CH₂Ph, C-5), 127.9, 128.3, 129.3 (3 d, Ph), 135.8 (s, Ph), 158.4, 169.0, 192.2 (3 s, C-2, C-3, C-6).

IR (KBr): ν = 3360 cm⁻¹ (N-H), 2960–2855 (C-H), 1745 (C=O), 1685 (C=O).

MS (EI, 80 eV, 190 °C): *m/z* (%) = 245 (100, [M]⁺), 106 (18), 91 (19, [Bn]⁺).

HRMS (EI, 80 eV) *m/z* calculated for [M⁺, C₁₄H₁₅NO₃]: 245.10519, found: 245.10733.

7.3.4 Esterification reactions and protection of the amino group

Synthesis of Methyl 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoate (102)

Method A

E 38 (IV 339)

Starting amounts:

0.254 g (1.09 mmol) 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic acid (**96**)

CH₂N₂ in diethyl ether, prepared from 8 mmol of N-nitrosoourea

50 ml MeOH/H₂O 10:1

Procedure: 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic acid (**96**) was dissolved in a MeOH/H₂O 10:1 solution, in a new wide neck Erlenmeyer flask. The diethyl ether solution of diazomethane was slowly added while shaking until permanent yellow colour was developed.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 68 mg (25 %) of **102** as yellow oil - for analytical data see E33 (IV206)

Method B

E 39 (IV 192)

Starting amounts:

- 0.098 g (0.42 mmol) 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic acid (**96**)
0.21 ml (0.43 mmol) Me₃SiCHN₂, 2 M solution in hexanes
2.5 ml PhMe/MeOH 1:1

Procedure: 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic acid (**96**) was dissolved in a toluene/methanol 1:1 mixture and cooled to 0 °C, then the Me₃SiCHN₂ solution was added under argon. The reaction mixture was stirred 18 hours at room temperature; the solvent was removed under reduced pressure.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2

Yield: 27 mg (26 %) of **102** as yellow oil - for analytical data see E33 (IV206)

Synthesis of 3-{3-[(*tert*-Butoxycarbonyl)amino]imidazo[1,2-*a*]pyridin-2-yl}-3-methylbutanoic acid (106**)**

E 40 (IV 246)

Starting amounts:

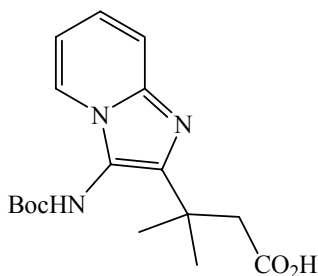
- 0.090 g (0.386 mmol) 3-(3-Aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic acid (**96**)
0.016 g (0.038 mmol) NaH (60%)
0.168 g (0.772 mmol) Boc₂O
cat. amt. DMAP
6 ml THF

Procedure: A stirred solution of 3-(3-aminoimidazo[1,2-*a*]pyridin-2-yl)-3-methylbutanoic acid (**96**) in tetrahydrofuran was treated with NaH, stirred for 1 h, treated with Boc₂O, stirred for another hour, treated with a catalytic amount of DMAP and stirred for one more hour. The

mixture was partitioned between ethyl acetate and saturated aqueous NH_4Cl solution and the organic phase was dried with Na_2SO_4 . The solvent was removed under reduced pressure.

Purification: Column chromatography on silica gel with 10% *i*-propanol/hexane

Yield: 100 mg (78 %) of **106** as brownish oil



106

$^1\text{H-NMR}$ (250 MHz, CDCl_3): δ = 1.36 (s, 6 H, Me), 1.49 (s, 9 H, CMe_3), 2.57 (s, 2 H, CH_2), 6.75 (t, J = 6.9 Hz, 1 H, 6-H), 7.07 (t, J = 6.9 Hz, 1 H, 7-H), 7.43–7.53 (m, 2 H, 8-H, 5-H).

$^{13}\text{C-NMR}$ (125.8 MHz, CDCl_3): δ = 26.0 (q, Me), 27.7, 85.2 (q, s, CMe_3), 31.6 (s, CMe_2), 50.4 (t, CH_2), 111.8 (d, C-6), 117.5 (d, C-8), 118.0 (s, C-3), 122.7 (d, C-5), 123.0 (d, C-7), 140.4 (s, C-2), 142.3 (s, C-8a), 148.5, 172.4 (2 s, C=O).

IR (KBr): ν = 3445 cm^{-1} (N-H), 3050–2875 (C-H), 1785, 1740 (C=O), 1635 (C=N), 1290 (C-O).

MS (EI, 80 eV, 100 °C): m/z (%) = 315 (2, $[\text{M} - \text{H}_2\text{O}]^+$), 215 (62), 200 (100), 78 (15), 57 (27).

HRMS (EI, 80 eV) m/z calculated for $[\text{M}^+ - \text{H}_2\text{O}, \text{C}_{17}\text{H}_{21}\text{N}_3\text{O}_3]$: 315.15829, found: 315.15733.

7.3.5 Synthesis of novel peptidomimetics 107 and 108

Synthesis of Methyl *N*-(3-{3-[(*tert*-Butoxycarbonyl)amino]imidazo[1,2-*a*]pyridin-2-yl}-3-methylbutanoyl)-*L*-alaninate (107)

E 41 (IV 251)

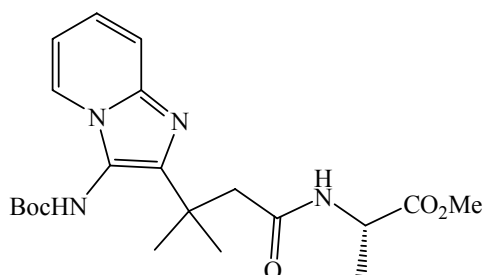
Starting amounts:

0.074 g	(0.222 mmol)	3-{3-[(<i>tert</i> -Butoxycarbonyl)amino]imidazo[1,2- <i>a</i>]pyridin-2-yl}-3-methylbutanoic acid (106)
0.036 g	(0.26 mmol)	L-Ala-OMe·HCl
0.115 g	(0.26 mmol)	BOP
0.1 ml	(0.66 mmol)	DIEA
2 ml		CH ₂ Cl ₂ , dry

Procedure: 3-{3-[(*tert*-Butoxycarbonyl)amino]imidazo[1,2-*a*]pyridin-2-yl}-3-methylbutanoic acid (**106**), H-Ala-OMe·HCl and BOP were dissolved in dry dichloromethane, and then DIEA was added. The reaction mixture was stirred at room temperature over 10 days. Ethyl acetate and water were added and the layers were separated. The organic layer was successively washed with saturated NaHCO₃ solution, brine and water, dried with Na₂SO₄ and the solvent was removed under reduced pressure.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 1:2, then methanol/dichloromethane 1:1, then HPLC (50 % *i*-propanol/hexane, 64 ml/min, 124 bar)

Yield: 89 mg (97 %) of **107** as colourless solid



107

Melting point: 70–72 °C

¹H-NMR (500 MHz, CDCl₃): δ = 1.06 (d, J = 7.2 Hz, 3 H, Me), 1.54, 1.55 (2 s, 9 H, 6 H, *CMe*₃, Me), 2.60–2.82 (m, 2 H, CH₂), 3.60 (s, 3 H, OMe), 4.35 (q, J = 7.2 Hz, 1 H, CH), 6.64, 6.74 (2 bs, 1 H, 1 H, NH), 6.82 (t, J = 6.2 Hz, 1 H, 6-H), 7.11–7.24 (m, 1 H, 7-H), 7.52 (d, J = 9.0 Hz, 1 H, 8-H), 7.86 (d, J = 6.2 Hz, 1 H, 5-H).

¹³C-NMR (125.8 MHz, CDCl₃): δ = 17.7, 28.2 (2 q, Me, *CMe*₃), 36.0 (s, *CMe*₂), 47.7 (d, CH), 50.6 (t, CH₂), 52.1 (q, OMe), 81.3 (s, *CMe*₃), 112.0 (d, C-6), 117.0 (d, C-8), 122.9 (d, C-5), 124.7 (d, C-7), 128.0 (s, C-3), 142.5 (s, C-2), 148.7 (s, C-8a), 154.1, 171.4, 171.5 (3 s, C=O).

IR (KBr): ν = 3290 cm⁻¹ (N-H), 3055–2880 (C-H), 1725 (C=O), 1655 (C=N).

MS (EI, 80 eV, 100 °C): m/z (%) = 418 (6, [M]⁺), 345 (15), 344 (48), 318 (39), 260 (12), 242 (20), 223 (14), 216 (15), 215 (71), 214 (45), 201 (11), 200 (85), 188 (57), 175 (13), 174 (100), 173 (14), 158 (13), 147 (11), 145 (10), 121 (12), 79 (12), 78 (30), 57 (32).

HRMS (EI, 80 eV) m/z calculated for [M⁺, C₂₁H₃₀N₄O₅]: 418.22162, found: 418.22351.

Optical rotation: $[\alpha]_D^{20}$ = -27.4 (c = 0.95, MeOH).

Synthesis of Methyl 3-(3-{[*N*-(*tert*-Butoxycarbonyl)-*L*-alanyl]amino}imidazo[1,2-*a*]pyridin-2-yl)propanoate (108)

E 42 (IV 304)

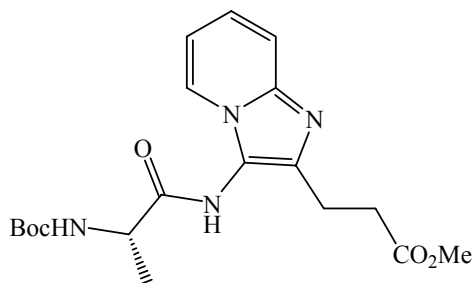
Starting amounts:

0.026 g	(0.12 mmol) Methyl 3-(3-Aminoimidazo[1,2- <i>a</i>]pyridin-2-yl)propanoate (101)
0.022 g	(0.12 mmol) Boc-Ala-OH
0.042 g	(0.15 mmol) TFFH
0.06 ml	(0.36 mmol) DIEA
3 ml	CH ₂ Cl ₂ , dry

Procedure: Methyl 3-(3-aminoimidazo[1,2-*a*]pyridin-2-yl)propanoate (**101**), Boc-Ala-OH and DIEA were dissolved in dry dichloromethane, cooled in an ice bath, then TFFH was added. The temperature was allowed to rise to room temperature; the reaction mixture was stirred over 4 days. The reaction mixture was successively washed with 1 M HCl, saturated NaHCO₃ solution and brine, dried with Na₂SO₄ and the solvent was removed under reduced pressure.

Purification: Column chromatography on silica gel with hexane/ethyl acetate 4:1, then methanol/dichloromethane 4:1, then HPLC (50 % *i*-propanol/hexane, 64 ml/min, 124 bar)

Yield: 12 mg (26 %) of **108** as pale yellow oil



108

¹H-NMR (500 MHz, CDCl₃): δ = 1.46 (s, 9 H, CMe₃), 1.55 (d, J = 7.2 Hz, 3 H, Me), 2.75–2.82 (m, 2 H, CH₂), 2.91–2.97 (m, 2 H, CH₂), 3.60 (s, 3 H, OMe), 4.43 (q, J = 7.2 Hz, 1 H, CH), 5.15 (bs, 1 H, NH), 6.75 (td, J = 6.8, 1.1 Hz, 1 H, 6-H), 7.13 (ddd, J = 9.0, 6.8, 1.1 Hz, 1 H, 7-H), 7.46 (dt, J = 9.0, 1.1 Hz, 1 H, 8-H), 7.73 (d, J = 6.8 Hz, 1 H, 5-H), 8.75 (bs, 1 H, NH).

¹³C-NMR (125.8 MHz, CDCl₃): δ = 18.2 (q, Me), 21.9 (t, CH₂), 28.3 (q, CMe₃), 33.0 (t, CH₂), 38.6 (s, CMe₂), 50.6 (d, CH), 51.7 (q, OMe), 80.3 (s, CMe₃), 111.8 (d, C-6), 115.5 (s, C-3), 117.1 (d, C-8), 123.6 (d, C-5), 124.2 (d, C-7), 138.6 (s, C-2), 142.8 (s, C-8a), 155.8, 172.7, 174.6 (3 s, C=O).

IR (KBr): ν = 3295 cm⁻¹ (N-H), 3055–2855 (C-H), 1715 (C=O), 1635 (C=N).

MS (EI, 80 eV, 150 °C): m/z (%) = 390 (15, [M]⁺), 334 (12), 290 (10), 247 (13), 246 (86), 219 (56), 218 (18), 214 (16), 187 (10), 186 (20), 160 (38), 159 (14), 146 (15), 144 (11), 131

(15), 80 (11), 79 (42), 73 (19), 59 (29), 57 (100), 56 (11), 55 (16), 44 (59), 43 (42), 41 (45), 39 (11), 31 (11), 29 (24), 28 (35).

HRMS (EI, 80 eV) m/z calculated for $[M^+, C_{19}H_{26}O_5N_4]$: 390.19031, found: 390.191444.

Optical rotation: $[\alpha]_D^{20} = -25.6$ (c = 0.09, MeOH).