Supporting Information

A One-Pot, Multicomponent Route to Pyrazoloquinolizinones

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EXPERIMENTAL SECTION

General Remarks:

Melting points of all compounds synthesized were determined with a Kofler or Gallenkamp melting point apparatus. The NMR spectra were recorded in DMSO- d_6 at 360 MHz (90,5 MHz for ^{13}C) with a Bruker AMX-360 and at 200 MHz (50 MHz for ^{13}C) with a Varian Mercury VX-200 spectrometer. 2D NMR spectra were measured at 600 MHz with Bruker spectrometer. The MS spectra were measured on a GC-MS Varian 1200L (ionizing voltage 70 eV) instrument. Elemental analysis was realized on EuroVector EA-3000.

All microwave experiments were performed using the EmrysTM Creator EXP, EmrysTM Synthesizer and EmrysTM Initiator 8 reactors from Biotage AB (Uppsala, Sweden) possessing a single-mode microwave cavity producing controlled irradiation at 2.45 GHz. Experiments were carried out in sealed microwave process vials utilizing the high absorbance level. Reaction time reflects irradiation times at the set reaction temperature (fixed hold times).

General procedures for the synthesis of 5a-hydroxy-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9-ones.

Method A (one pot, one-step): An equimolar mixture of the appropriate 5-aminopyrazole **6** (0.7 mmol), cyclic 1,3-diketone **7** (0.7 mmol) and of the corresponding aromatic aldehyde **8** (0.7 mmol) in 3 mL of EtOH containing powdered KOH (0.7 mmol) was irradiated under sealed vessel microwave conditions at 150 °C for 25 min in a 5 mL microwave process vial. Then the solvent was removed by evaporation and 4 mL of an EtOH-H₂O mixture (1:1) was added to the residue and heated with vigorous stirring. After cooling the formed crystals were removed by filtration, washed with EtOH-H₂O (1:1) and dried in air.

Method B (one-pot, one-step): A mixture of the appropriate 5-aminopyrazole **6** (0.7 mmol), cyclic 1,3-diketone **7** (1.4 mmol), corresponding aromatic aldehyde **8** (0.7 mmol), and of sodium ethoxide (1.4 mmol) in 3 mL of EtOH was irradiated under sealed vessel microwave conditions at 150 °C for 20 min in a 5 mL microwave process vial. Then the solvent was removed by evaporation and 4 mL of EtOH-H₂O mixture (1:1) was added to the residue and heated with vigorous stirring. After cooling the formed crystals were removed by filtration, washed with EtOH-H₂O (1:1) and dried in air.

Method C (one-pot, two-step): A mixture of the cyclic 1,3-diketone **7** (1.4 mmol), the corresponding aromatic aldehyde **8** (0.7 mmol) and of sodium ethoxide (1.4 mmol) in 2 mL of EtOH was irradiated under sealed vessel microwave conditions at 100 °C for 2 min in a 5 mL microwave process vial. Then the appropriate 5-aminopyrazole **6** (0.7 mmol) dissolved in 1 mL of EtOH was added to the vial and the reaction mixture was MW irradiated again at 150 °C for 15 min. Then the solvent was removed by evaporation and 4 mL of EtOH-H₂O mixture (1:1) was added to the residue and heated with vigorous stirring. After cooling the formed crystals were removed by filtration, washed with EtOH-H₂O (1:1) and dried in air.

Method D (one-pot, two-step): A mixture of the appropriate 5-aminopyrazole **6** (0.7 mmol), the corresponding aromatic aldehyde **8** (0.7 mmol) and of sodium ethoxide (0.7 mmol) in 2 mL of EtOH was irradiated under sealed vessel microwave conditions at 150 °C for 10 min in a 5 mL microwave process vial. Then the cyclic 1,3-diketone **7** (0.7 mmol) dissolved in 1 mL of EtOH was added to the vial and the reaction mixture was MW irradiated again at 150 °C for 10 min. Then the solvent was removed by evaporation and 4 mL of EtOH-H₂O mixture (1:1) was added to the residue and heated with vigorous stirring. After cooling the formed crystals were removed by filtration, washed with EtOH-H₂O (1:1) and dried in air.

(5a-hydroxy-7,7-dimethyl-3,4-diphenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9a):

Mp: 238-240 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 0.97 (s, 3H), 1.18 (s, 3H), 1.80 (dd, 1H, *J* = 11.6 Hz & 13.6), 1.93 (s, 2H), 2.28 (dd, 1H, *J* = 6.0 Hz & 13.6 Hz), 2.33-2.47 (dd, 2H), 4.43 (dd, 1H, *J* = 6.0 Hz & 11.3 Hz), 6.09 (br s, 1H, D₂O-exchangeable), 6.85-7.20 (m, 5H), 7.21-7.42 (m, 3H), 7.52 (m, 2H), 12.57 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 90 MHz): δ 28.95, 29.71, 30.27, 35.48, 48.28, 49.55, 84.97, 103.76, 126.35, 126.41, 127.41, 127.82, 127.94, 128.49, 129.16, 144.29,

148.02, 152.62; MS (EI, 70 eV), (m/z): 387 (75.8) [M], 388 (15.8) [M+H], 294 (100); Anal calc'd for C₂₄H₂₅N₃O₂: C, 74.39; H, 6.50; N, 10.84; Found: C, 74.13; H, 6.41; N, 10.87.

(5a-hydroxy-7,7-dimethyl-4-(4-methylphenyl)-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9b):

Mp: 265-267 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 0.96 (s, 3H), 1.17 (s, 3H), 1.77 (dd, 1H, *J* = 13.6 Hz & 11.3), 1.89 (d, 1H), 1.95 (d, 1H), 2.11 (s, 3H), 2.26 (dd, 1H, *J* = 6.0 Hz & 13.6 Hz), 2.37(d, 1H, *J* = 16.3 Hz), 2.46 (d, 1H, *J* = 16.3 Hz), 4.40 (dd, 1H, *J* = 6.0 Hz & 11.3 Hz), 6.09 (br s, 1H, D₂O-exchangeable), 6.78-6.99 (m, 4H), 6.99-7.12 (m, 3H), 7.30-7.45 (m, 2H), 12.83 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 90 MHz): δ 21.00, 28.94, 29.71, 30.25, 35.07, 46.69, 48.31, 49.76, 84.97, 126.96, 127.36, 127.76, 127.88, 128.67, 129.13, 135.08, 141.34, 168.44; MS (EI, 70 eV), (m/z): 403 (26), 402 (100) [M+H], 385 (25), 284 (80); Anal calc'd for C₂₅H₂₇N₃O₂: C, 74.79; H, 6.78; N, 10.47; Found: C, 74.50; H, 6.75; N, 10.50.

(5a-hydroxy-4-(4-methoxyphenyl)-7,7-dimethyl-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9c):

Mp: 256-258 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 0.96 (s, 3H), 1.16 (s, 3H), 1.76 (dd, 1H, *J* = 11.6 & 13.0 Hz), 1.89 (d, 2H), 2.24 (dd, 1H, *J* = 6.0 Hz & 13.6 Hz), 2.36 (d, 1H, *J* = 16.6 Hz), 2.45 (d, 1H, *J* = 16.6 Hz), 3.58 (s, 3H), 4.38 (dd, 1H, *J* = 6.0 Hz & 11.6 Hz), 6.04 (br s, 1H, D₂O-exchangeable), 6.55-6.67 (m, 2H), 6.89-6.99 (m, 2H), 7.00-7.12 (m, 3H), 7.30-7.39 (m, 2H), 12.78 (br s, 1H, D₂O-exchangeable); ¹³C NMR (DMSO-*d*₆, 90 MHz): δ 28.98, 29.71, 30.25, 34.61, 46.69,

48.35, 49.79, 55.33, 85.01, 104.19, 113.96, 126.96, 127.46, 127.84, 128.86, 136.18, 157.78, 168.47; MS (EI, 70 eV), (m/z): 417 (86.7) [M], 418 (26.4) [M+H], 400 (9.1) [M-OH], 399 (29.9), 398 (55.6); Anal calc'd for C₂₅H₂₇N₃O₃: C, 71.92; H, 6.52; N, 10.06; Found: C, 71.71; H, 6.57; N, 9.99.

(4-(4-bromophenyl)-5a-hydroxy-7,7-dimethyl-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9d):

Mp: 258-260 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 0.951 (s, 3H), 1.16 (s, 3H), 1.75 (dd, 1H, *J* = 11.9 & 11.3 Hz), 1.87-1.95 (m, 2H), 2.25 (dd, 1H, *J* = 11.9 Hz & 11.1 Hz), 2.40 (d, 2H, *J* = 6.3 Hz), 4.34 (dd, 1H, *J* = 11.3 Hz & 11.1 Hz), 6.08 (br s, 1H, D₂O-exchangeable), 6.93-7.38 (m, 9H), 12.76 (br s, 1H, D₂O-exchangeable); MS (EI, 70 eV), (m/z): 465 (8.0) [M], 292 (100); Anal calc'd for C₂₄H₂₄BrN₃O₂: C, 61.81; H, 5.19; Br, 17.13; N, 9.01; Found: C, 61.58; H, 5.25; Br, 17.07; N, 9.04.

(4-(4-fluorophenyl)-5a-hydroxy-7,7-dimethyl-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9e):

Mp: 243-245 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 0.96 (s, 3H), 1.17 (s, 3H), 1.79 (dd, 1H, *J* = 11.6 Hz & 13.6 Hz), 1.93 (dd, 2H), 2.26 (dd, 1H, *J* = 6.0 Hz & 13.6 Hz), 2.37 (d, 2H, *J* = 16.6 Hz), 2.46 (d, 2H, *J* = 16.6 Hz), 4.45 (dd, 1H, *J* = 6.0 Hz & 11.6 Hz), 6.09 (s, 1H), 6.80-6.90 (m, 2H), 7.00-7.12 (m, 5H), 7.31 (m, 2H), 12.77 (s, 1H); ¹³C NMR (DMSO-*d*₆, 90 MHz): δ 28.98, 29.71, 30.26, 34.70, 46.62, 48.26, 49.35, 84.98, 103.68, 115.00, 115.23, 127.00, 127.52, 127.84, 129.69, 134.33, 138.32, 140.31, 146.62, 159.51, 168.56; MS (EI, 70 eV), (m/z): 405 (79.9) [M], 406 (21.1)

[M+H], 292 (100); Anal calc'd for C₂₄H₂₄N₃O₂: C, 71.09; H, 5.97; N, 10.36; Found: C, 70.87; H, 6.02; N, 10.39.

(5a-hydroxy-3,4-diphenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9f):

Mp: 285-287 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 1.62-1.73 (m, 1H), 1.79 (dd, 1H, *J* = 11.3 Hz & 13.6 Hz), 1.83-1.98 (m, 2H), 2.08-2.21 (m, 1H), 2.27 (dd, 1H, *J* = 6.0 Hz & 13.6 Hz), 2.51 (d, 1H, *J* = 4.0 Hz), 2.56 (d, 1H, *J* = 4.0 Hz), 4.43 (dd, 1H, *J* = 6.0 Hz & 11.3 Hz), 6.35 (b.s, 1H, D₂O-exchangeable), 6.90-7.19 (m, 8H), 7.28-7.38 (dd, 2H, *J* = 7.6 Hz & 7.6 Hz), 12.80 (br s, 1H, D₂O-exchangeable); ¹³C NMR (DMSO-*d*₆, 90 MHz): δ 15.44, 33.23, 35.30, 35.76, 48.28, 84.53, 103.60, 126.31, 126.92, 127.46, 127.78, 127.95, 128.45, 134.22, 144.38, 168.57; MS (EI, 70 eV), (*m/z*): 359 (100) [M], 282 (42.1) ; Anal calc'd for C₂₂H₂₁N₃O₂: C, 73.52; H, 5.89; N, 11.69; Found: C, 73.76; H, 5.93; N, 11.72.

(5a-hydroxy-4-(4-methylphenyl)-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9g):

Mp: 310-312 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 1.61-1.80 (m, 2H), 1.81-1.97 (m, 2H), 2.10 (s, 3H), 2.14-2.22 (m, 1H), 2.24 (dd, 1H, *J* = 6.0 Hz & 13.6 Hz), 2.48 (d, 1H, *J* = 3.6 Hz), 2.51 (d, 1H, *J* = 3.6 Hz), 4.40 (dd, 1H, *J* = 6.0 Hz & 11.3 Hz), 6.25 (br s, 1H, D₂O-exchangeable), 6.86 (d, 2H, *J* = 8.0 Hz), 6.94 (d, 2H, *J* = 8.0 Hz), 6.99-7.11 (m, 4H), 7.31-7.40 (m, 2H), 12.84 (br s, 1H); ¹³C NMR (DMSO-*d*₆, 90 MHz): δ 15.44, 21.00, 33.23, 34.90, 35.78, 48.49, 84.51, 103.74, 126.37, 126.93, 127.39, 127.75, 127.84, 128.53, 129.08, 134.28, 135.03, 141.44, 168.54; MS (EI, 70 eV), (*m/z*): 373

(100) [M], 374 (23.5) [M+H], 264 (54.8); Anal calc'd for C₂₃H₂₃N₃O₂: C, 73.97; H, 6.21; N, 11.25; Found: C, 73.75; H, 6.19; N, 11.28.

(5a-hydroxy-4-(4-methoxyphenyl)-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9h):

Mp: 298-300 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 1.60-1.80 (m, 2H), 1.81-1.98 (m, 2H), 2.06-2.20 (m, 2H), 2.23 (dd, 1H, *J* = 6.0 Hz & 13.9 Hz), 2.52-2.56 (m, 2H), 3.58 (s, 3H), 4.38 (dd, 1H, *J* = 6.0 Hz & 11.6 Hz), 6.24 (s, 1H), 6.61 (d, 2H, *J* = 8.6 Hz), 6.96 (d, 2H, *J* = 8.6 Hz), 7.00-7.10 (m, 3H), 7.35 (m, 2H), 12.74 (s, 1H); ¹³C NMR (DMSO-*d*₆, 90 MHz): δ 15.43, 33.21, 34.43, 35.73, 48.50, 55.33, 84.54, 113.91, 126.90, 127.48, 127.78, 128.85, 134.38, 136.03, 136.12, 136.29, 157.75; MS (EI, 70 eV), (*m/z*): 389 (100) [M], 390 (16.5) [M+H], 264 (58.6); Anal calc'd for C₂₃H₂₃N₃O₃: C, 70.93; H, 5.95; N, 10.79; Found: C, 70.71; H, 5.90; N, 10.82.

(4-(4-bromophenyl)-5a-hydroxy-3-phenyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9i):

Mp: 252-254 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 1.57-1.81 (m, 2H), 1.82-2.00 (m, 2H), 2.08-2.21 (m, 2H), 2.26 (dd, 1H, *J* = 6.0 Hz & 13.6 Hz), 2.53-2.59 (m, 2H), 4.45 (dd, 1H, *J* = 6.0 Hz & 11.3 Hz), 6.33 (br s, 1H, D₂O-exchangeable), 6.96-7.14 (m, 5H), 7.18-7.26 (m, 2H), 7.28-7.38 (m, 2H), 12.78 (br s, 1H, D₂O-exchangeable); ¹³C NMR (DMSO-*d*₆, 90 MHz): δ 15.43, 33.23, 34.77, 35.74, 47.88, 84.53, 103.18, 119.90, 126.33, 127.10, 127.49, 127.92, 128.62, 130.24, 131.28, 143.95,

168.59; MS (EI, 70 eV), (m/z): 437 (33.8) [M], 438 (7.3) [M+H], 439 (38.5) [M+2+H]⁺, 264 (100); Anal calc'd for C₂₂H₂₀BrN₃O₂: C, 60.28; H, 4.60; Br, 18.23; N, 9.59; Found: C, 60.45; H, 4.65; Br, 18.18; N, 9.63.

(4-(4-bromophenyl)-5a-hydroxy-3,7,7-trimethyl-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9j):

Mp: 245-247 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 0.96 (s, 3H), 1.14 (s, 3H), 1.51 (s, 3H), 1.75-1.98 (m, 3H), 2.16 (dd, *J* = 5.6 Hz & 13.3 Hz, 1H), 2.32 (d, 1H, *J* = 16.6 Hz), 2.43 (d, 1H, *J* = 16.6 Hz), 4.02 (dd, 1H, *J* = 5.6 Hz & 11.6 Hz), 5.93 (br s, 1H, D₂O-exchangeable), 7.16 (d, 2H, *J* = 8.3 Hz), 7.49 (d, 2H, *J* = 8.3 Hz), 12.15 (br s, 1H, D₂O-exchangeable); ¹³C NMR (DMSO-*d*₆, 90 MHz): δ 13.41, 19.04, 27.40, 29.09, 29.71, 30.33, 32.39, 34.27, 35.23, 46.61, 47.89, 48.44, 50.88, 85.18, 119.74, 129.96, 130.60, 131.04, 131.84, 143.68, 148.25, 153.37, 168.41; MS (EI, 70 eV), (m/z): 403 (16.5) [M], 404 (19.1) [M+H]; Anal calc'd for C₁₉H₂₂BrN₃O₂: C, 56.44; H, 5.48; Br, 19.76; N, 10.39; Found: C, 56.60; H, 5.49; Br, 16.68; N, 10.33.

(5a-hydroxy-3-methyl-4-phenyl)-4,5,5a,6,7,8-hexahydropyrazolo[4,3-c]quinolizin-9(1H)-one) (9k):

Mp: 258-260 °C; ¹H NMR (DMSO-*d*₆, 360 MHz): δ 1.47 (s, 3H), 1.60-1.72 (m, 1H), 1.78-1.96 (m, 3H), 2.15 (dd, 1H, *J* = 5.6 Hz & 13.6 Hz), 2.47 (m, 2H), 4.02 (dd, 1H, *J* = 5.6 Hz & 11.9 Hz), 6.15 (br s, 1H), 7.14-7.27 (m, 3H), 7.27-7.35 (m, 2H), 12.12 (br s, 1H, D₂O-exchangeable); ¹³C NMR

(DMSO-*d*₆, 90 MHz): δ 13.34, 15.39, 33.12, 34.59, 35.88, 46.82, 84.81, 104.37, 126.87, 128.34, 128.93, 144.20, 168.48; MS (EI, 70 eV), (m/z): 297 (84.7) [M], 298 (14.7) [M+H], 202 (100); Anal calc'd for C₁₉H₂₃N₃O₂: C, 68.67; H, 6.44; N, 14.13; Found: C, 68.91; H, 6.48; N, 14.07.

ROESY
spectrum for
compounds **9b**

S19

Molecular Structure (X-ray Diffraction Data) of 9d

Spectrum 1A

A-149

BP 230 (1.420e+8=100%) a-149-dep_15.01.2007.xms 0.325 min. Scans: 33-39 Channel: 1 Ion: NA RIC: 6.143e+8

Spectrum 1A

A-196

BP 202 (9.233e+7=100%) a-196-dep_15.01.2007.xms

0.331 min. Scan: 37 Channel: 1 Ion: NA RIC: 5.715e+8