A Multicomponent Reaction for the One-Pot Synthesis of

4-Aza-2,3-dehydropodophyllotoxin and derivatives

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Experimental part

Supporting information

General synthesis of 4-aza-2,3-dehydropodophyllotoxins

A equimolecular mixture of tetronic acid **2**, an aniline, an aromatic aldehyde in solution in the minimum of ethanol was refluxed for x min. After cooling, the precipitate was filtered off, washed with ethanol, and then purified.

4,9-Dihydro-6,7-methylenedioxy-9-(3,4,5-trimethoxyphenyl)furo[3,4-*b*]quinolin-1(3*H*)-one (6a)

x: 10 min; purification: recrystallization from ethanol; yield: 92 %. Mp > 260 °C (lit.⁵: 271-274 °C). IR (KBr): 3155, 1728, 1648, 1613, 1590, 1552, 1480, 1239, 1190, 1128, 1032, 1016 cm⁻¹. ¹H NMR (DMSO-d₆, 300 MHz): δ 3.60(s, 3H), 3.72 (s, 6H), 4.85 (m, 2H), 5.00 (d, *J* = 15 Hz, 1H), 5.90 (s, 1H), 5.95 (s, 1H), 6.45 (s, 2H), 6.50 (s, 1H), 6.65 (s, 1H), 9.85 (bs, 1H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 41.1, 56.9, 61.0, 66.1, 95.2, 98.4, 102.3, 105.9, 110.7,

2

117.7, 131.4, 137.1, 143.9, 144.3, 147.6, 153.9, 159.6, 173.2. Microanalysis (%): found : C 63.32, H 4.86, N 3.45; calcd. for $C_{21}H_{19}NO_7$: C 63.47, H 4.82, N 3.52.

4,9-Dihydro-4-methyl-6,7-methylenedioxy-9-(3,4,5-trimethoxyphenyl)furo[3,4-*b*]quinolin-1(3*H*)-one (6b)

x: 10 min; purification: recrystallization from ethanol; yield: 80 %. Mp 226 °C. IR (KBr): 1734, 1654, 1611, 1591, 1483, 1238, 1204, 1124, 1039 cm^{-1} . 1H NMR ($CDCl_3$, 300 MHz): δ 3.25 (s, 3H), 3.80 (s, 9H), 4.80 (d, $J = 15$ Hz, 1H), 4.90 (d, $J = 15$ Hz, 1H), 5.05 (s, 1H), 5.95 (s, 1H), 5.97 (s, 1H), 6.40 (s, 2H), 6.60 (s, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 36.6, 40.7, 56.1, 60.7, 65.0, 94.9, 97.4, 101.6, 105.1, 110.6, 118.2, 133.3, 136.7, 141.5, 144.1, 147.5, 153.1, 158.0, 172.6. Microanalysis (%): found : C 64.11, H 5.09, N 3.26; calcd. for $C_{22}H_{21}NO_7$: C 64.23, H 5.14, N 3.40.

4,9-Dihydro-4-(3,3-dimethylaminopropyl)-6,7-methylenedioxy-9-(3,4,5-trimethoxyphenyl)furo[3,4-*b*]quinolin-1(3*H*)-one, hydrochloride (6c)

x: 10 min; purification: recrystallization from ethanol; yield: 45 %. Mp 182 °C. IR (KBr): 1734, 1650, 1612, 1587, 1508, 1470, 1239, 1127 cm^{-1} . 1H NMR ($CDCl_3$, 300 MHz): δ 1.75 (m, 2H), 2.10 (s, 6H), 2.15 (m, 1H), 2.25 (m, 1H), 3.50 (m, 1H), 3.60 (m, 1H), 3.70 (s, 9H), 4.75 (d, $J = 15$ Hz, 1H), 4.75 (s, 1H), 4.95 (d, $J = 15$ Hz, 1H), 5.80 (s, 1H), 5.85 (s, 1H), 6.30 (s, 2H), 6.40 (s, 1H), 6.55 (s, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.2, 40.6, 43.4, 45.0, 55.2, 55.9, 60.6, 65.4, 95.4, 96.8, 101.4, 104.7, 110.6, 118.6, 131.3, 136.4, 141.8, 143.9, 147.4, 153.0, 158.3, 172.8. Microanalysis (%): found : C 56.31, H 5.94, N 4.85; calcd. for $C_{26}H_{31}ClN_2O_7 \cdot 2H_2O$: C 56.26, H 6.36, N 5.05.

4,9-Dihydro-6-hydroxy -9-(3,4,5-trimethoxyphenyl)furo[3,4-*b*]quinolin-1(3*H*)-one (12a)

x: 45 min; purification: flash chromatography on silica gel (solvent: dichloromethane:methanol 8:2); yield: 63 %. Mp > 260 °C. IR (KBr): 3365, 3318, 1731, 1653, 1624, 1594, 1491, 1462, 1334, 1118, 1011 cm⁻¹. ¹H NMR (DMSO-d₆, 300 MHz): δ 3.55 (s, 3H), 3.65 (s, 6H), 4.80 (d, *J* = 15 Hz, 1H), 4.82 (s, 1H), 4.95 (d, *J* = 15 Hz, 1H), 6.30 (m, 2H), 6.40 (s, 2H), 6.85 (d, *J* = 8 Hz, 1H), 9.35 (bs, 1H), 9.85 (bs, 1H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 41, 56.8, 60.9, 65.9, 96.4, 103.5, 111.9, 115.9, 132.4, 137.9, 143.9, 153.7, 157.6, 159.5, 173.2. Microanalysis (%): found : C 64.71, H 5.24, N 3.62; calcd. for C₂₀H₁₉NO₆: C 65.03, H 5.18, N 3.79.

4,9-Dihydro-6,7-dimethoxy-9-(3,4,5-trimethoxyphenyl)furo[3,4-*b*]quinolin-1(3*H*)-one (12b)

x: 10 min; purification: recrystallization from ethanol; yield: 94 %. Mp 219-221 °C (lit.⁵: 236-238 °C). IR (KBr): 3274, 1720, 1637, 1546, 1509, 1643, 1198, 1103, 1029 cm⁻¹. ¹H NMR (DMSO-d₆, 300 MHz): δ 3.55 (m, 6H), 3.70 (s, 6H), 3.75 (s, 3H), 4.85 (d, *J* = 15 Hz, 1H), 4.90 (s, 1H), 4.95 (d, *J* = 15 Hz, 1H), 6.45 (s, 2H), 6.48 (s, 1H), 6.70 (s, 1H), 9.80 (bs, 1H). ¹³C NMR (DMSO-d₆, 75 MHz): δ 56.8, 57.2, 60.9, 66.3, 97.8, 102.5, 105.9, 106.9, 110.6, 119.2, 133.7, 13.7, 134.1, 143.3, 144.7, 147.6, 153.9, 155.0, 160.1, 173.0. Microanalysis (%): found : C 63.74, H 5.44, N 3.17; calcd. for C₂₂H₂₃NO₇: C 63.91, H 5.61, N 3.39.

4,11-Dihydro-11-(3,4,5-trimethoxyphenyl)benzo[7,8]furo[3,4-*b*]quinolin-1(3*H*)-one (12c)

x: 10 min; purification: recrystallization from ethanol; yield: 59 %. Mp > 260 °C. IR (KBr): 3282, 1753, 1672, 1595, 1529, 1509, 1209, 1125, 1034, 996 cm⁻¹. ¹H NMR (DMSO-d₆, 300 MHz): δ 3.58 (s, 3H), 3.62 (s, 6H), 4.90 (d, *J* = 15 Hz, 1H), 5.00 (d, *J* = 15 Hz, 1H), 5.60 (s, 1H), 6.50 (s, 2H), 7.32 (d, *J* = 8.7 Hz, 1H), 7.33-7.43 (m, 2H), 7.80 (m, 3H), 10.23 (bs, 1H).

^{13}C NMR (DMSO- d_6), 75 MHz): δ 41.2, 56.8, 60.9, 66.0, 98.1, 106.2, 115.5, 118.6, 124.3, 124.9, 127.9, 129.4, 130.0, 131.6, 132.9, 142.6, 153.7, 158.2, 173.1. Microanalysis (%): found: C 70.67, H 5.44, N 3.44; calcd. for $\text{C}_{24}\text{H}_{21}\text{NO}_5$: C 71.45, H 5.25, N 3.47.

4,9-Dihydro-6,7-methylenedioxy-9-(2,3,4-trimethoxyphenyl)furo[3,4-*b*]quinolin-1(3*H*)-one (12d)

x: 10 min; purification: recrystallization from ethanol; yield: 83 %. Mp > 260 °C. IR (KBr): 3276, 1720, 1651, 1625, 1558, 1482, 1283, 1188, 1092, 1030 cm^{-1} . ^1H NMR (DMSO- d_6 , 300 MHz): δ 3.75(s, 9H), 4.80 (d, J = 15 Hz, 1H), 4.90 (d, J = 15 Hz, 1H), 5.10 (s, 1H), 5.83 (s, 1H), 5.86 (s, 1H), 6.40 (s, 1H), 6.45 (s, 1H), 6.65 (d, J = 8 Hz, 1H), 6.70 (d, J = 8 Hz, 1H), 9.80 (bs, 1H). ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 34.4, 56.8, 61.4, 61.8, 65.9, 95.0, 98.3, 102.1, 109.3, 110.0, 118.6, 124.7, 131.4, 133.9, 142.7, 144.2, 147.3, 151.1, 152.9, 159.6, 173.1. Microanalysis (%): found : C 63.57, H 4.91, N 3.34; calcd. for $\text{C}_{21}\text{H}_{19}\text{NO}_7$: C 63.47, H 4.82, N 3.52.

4,9-Dihydro-6,7-methylenedioxy-9-(3-pyridyl)furo[3,4-*b*]quinolin-1(3*H*)-one (12e)

x: 30 min; flash chromatography on silica gel (solvent: ethyl acetate:methanol 9:2 to 8:2); yield: 78 %. Mp > 260 °C. IR (KBr): 3228, 1702, 1640, 1620, 1559, 1509, 1488, 1249, 1199, 1032, 930 cm^{-1} . ^1H NMR (DMSO- d_6 , 300 MHz): δ 4.85 (d, J = 16 Hz, 1H), 4.95 (d, J = 16 Hz, 1H), 5.02 (s, 1H), 5.88 (s, 1H), 5.95 (s, 1H), 6.50 (s, 1H), 6.55 (s, 1H), 7.25 (m, 1H), 7.50 (dd, J = 1 Hz, J = 6 Hz, 1H), 8.35 (dd, J = 1 Hz, J = 6 Hz, 1H), 8.45 (d, J = 1 Hz, 1H), 9.95 (bs, 1H). ^{13}C NMR (DMSO- d_6 , 75 MHz): δ 38.2, 66.1, 94.4, 98.4, 102.3, 110.5, 116.5, 124.7, 131.6, 136.1, 142.9, 144.5, 147.7, 148.5, 149.5, 159.6, 173.0. Microanalysis (%): found : C 64.14, H 4.15, N 8.61; calcd. for $\text{C}_{17}\text{H}_{12}\text{N}_2\text{O}_4 \cdot 0.5 \text{H}_2\text{O}$: C 64.35, H 4.13, N 8.83.