

SUPPLEMENTARY MATERIAL

SYNTHESIS OF DEUTERATED CYCLODOPA WITH HYDROGEN/DEUTERIUM EXCHANGE

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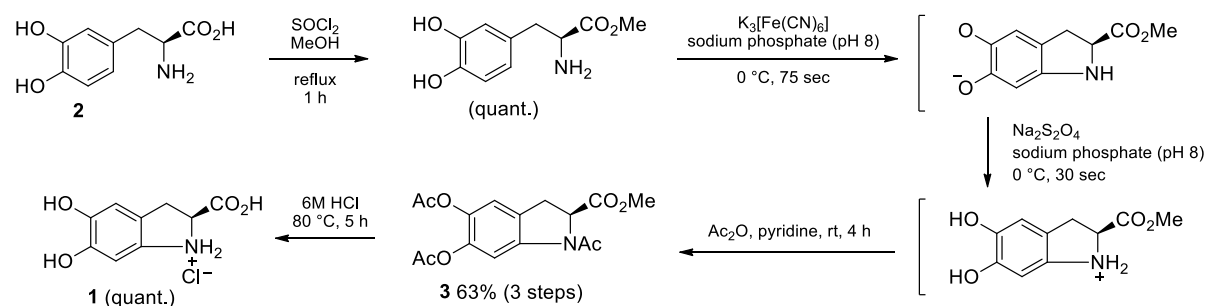
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SM-1. Synthesis of *O,O,N*-triacetyl cycloDOPA methyl ester (**3**) and cycloDOPA (**1**)

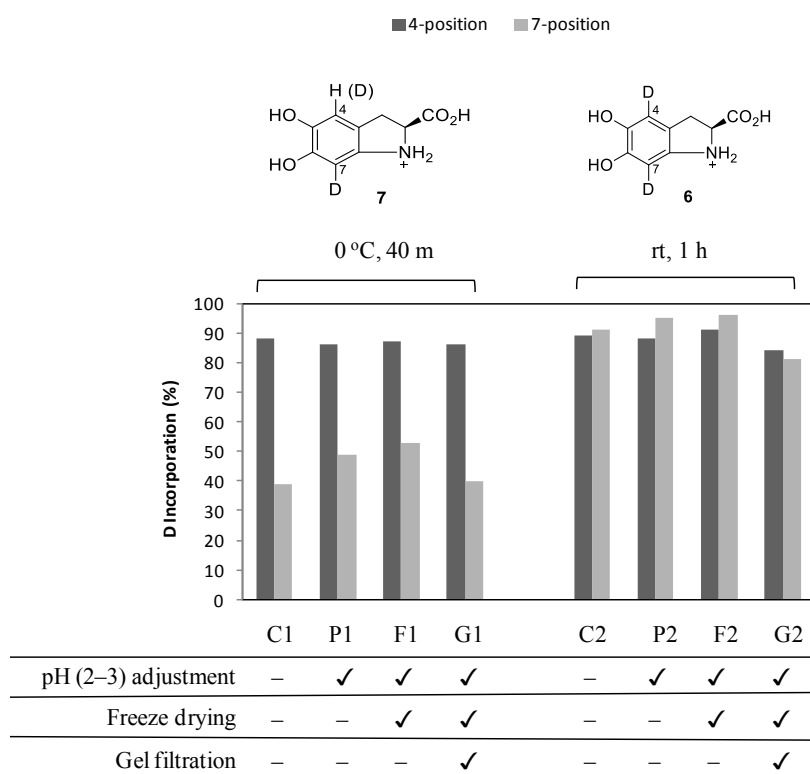


Scheme SM-1. Synthesis of *O,O,N*-triacetyl cycloDOPA methyl ester **3** and cycloDOPA **1** were followed previous reported study (*Molecules*, 2018, **23**, 1943).

***O,O,N*-triacetyl cycloDOPA methyl ester (3)**. Colorless amorphous mass. $[\alpha]_D = -73$ (c 1, CHCl₃), ¹H-NMR (270 MHz, CDCl₃) δ : 8.06 (1H, s), 6.99–6.95 (1H, m), 5.18 (0.3 H, d, $J = 8.6$ Hz), 4.94 (1H, d, $J = 8.6$ Hz), 3.78 (3H, s), 3.57 (1H, dd, $J = 17.0, 10.7$ Hz), 3.25 (1H, d, $J = 16.5$ Hz), 2.29–2.11 (9H, m) ppm. ¹³C-NMR (67.5 MHz, CDCl₃) δ : 171.0, 168.6, 168.0, 167.8, 140.7, 140.2, 137.7, 126.5, 118.5, 111.7, 61.2, 52.5, 32.4, 22.9, 20.0, 20.0 ppm. HRMS (ESI): calcd for C₁₆H₁₈NO₇ [M + H]⁺ 336.1083, found 336.1086.

cycloDOPA hydrochloride (1, cycloDOPA). Brown amorphous mass. $[\alpha]_D = -85$ (c 1.0, D₂O), ¹H-NMR (270 MHz, D₂O) δ : 6.90 (1H, s), 6.84 (1H, s), 4.85 (1H, dd, $J = 9.7, 6.8$ Hz), 3.50 (1H, dd, $J = 16.2, 9.6$ Hz), 3.27 (1H, dd, $J = 16.2, 6.6$ Hz) ppm. ¹³C-NMR (67.5 MHz, D₂O) δ : 171.6, 146.6, 145.0, 126.5, 125.6, 112.6, 106.9, 61.1, 33.0 ppm. HRMS (ESI): calcd for C₉H₁₀NO₄ [M + H]⁺ 196.0610, found 196.0612.

SM. 2 Excess TfOD removal trial for deuterated cycloDOPA derivatives (6 and 7)



Scheme SM-2. Excess TfOD removal trial for deuterated cycloDOPA derivatives (6 and 7)

Index:

C1: cDOPA **1** is treated with TfOD at 0 °C for 40 m and directly subjected into NMR.

P1: C2 after pH (2–3) adjustment by NaOD.

F1: P2 after overnight freeze drying.

G1: F1 after separation by gel filtration chromatography (Sephadex G-10 eluted by HCl (pH = 3), 27% recovery in Cl⁻ salt measured from UV-Vis spectra).

C2: cDOPA **1** is treated with TfOD at rt for 1 h and directly subjected into NMR.

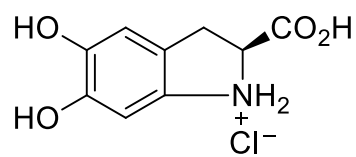
P2: C2 after pH (2–3) adjustment by NaOD.

F2: P2 after overnight freeze drying.

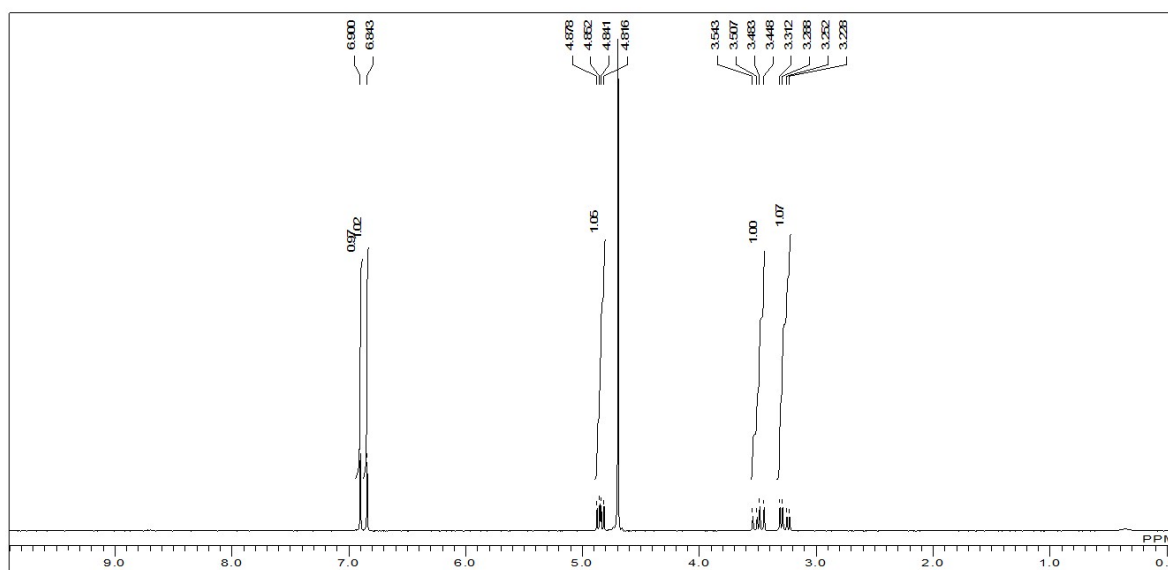
G2: F2 after separation by gel filtration chromatography (Sephadex G-10 eluted by HCl (pH = 3), 26% recovery in Cl⁻ salt measured from UV-Vis spectra).

SM. 3 NMR spectra

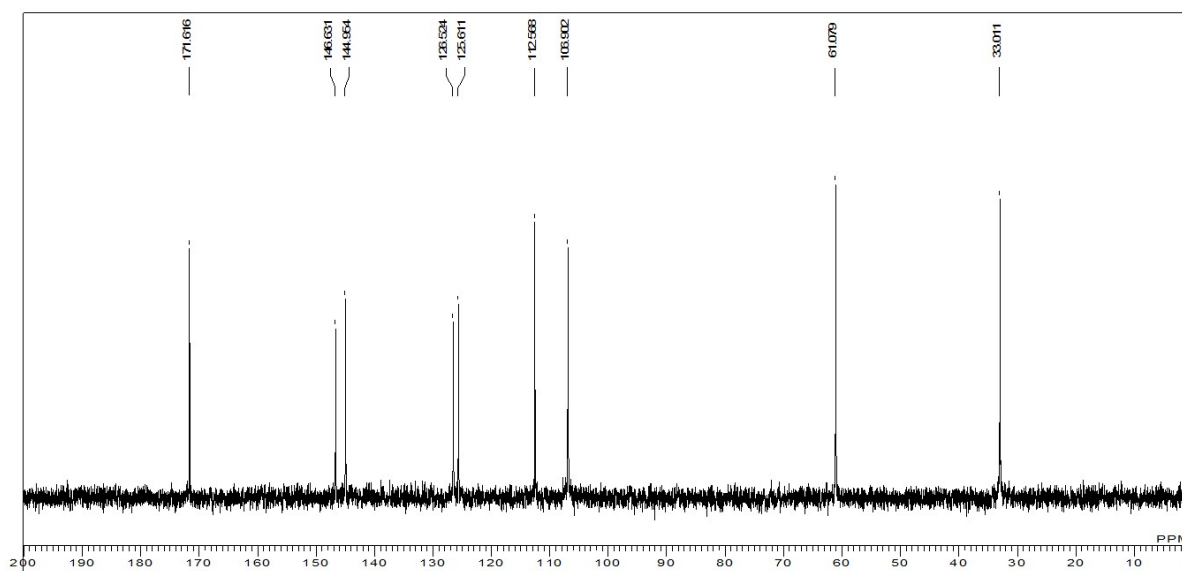
cycloDOPA hydrochloride (1, cycloDOPA)



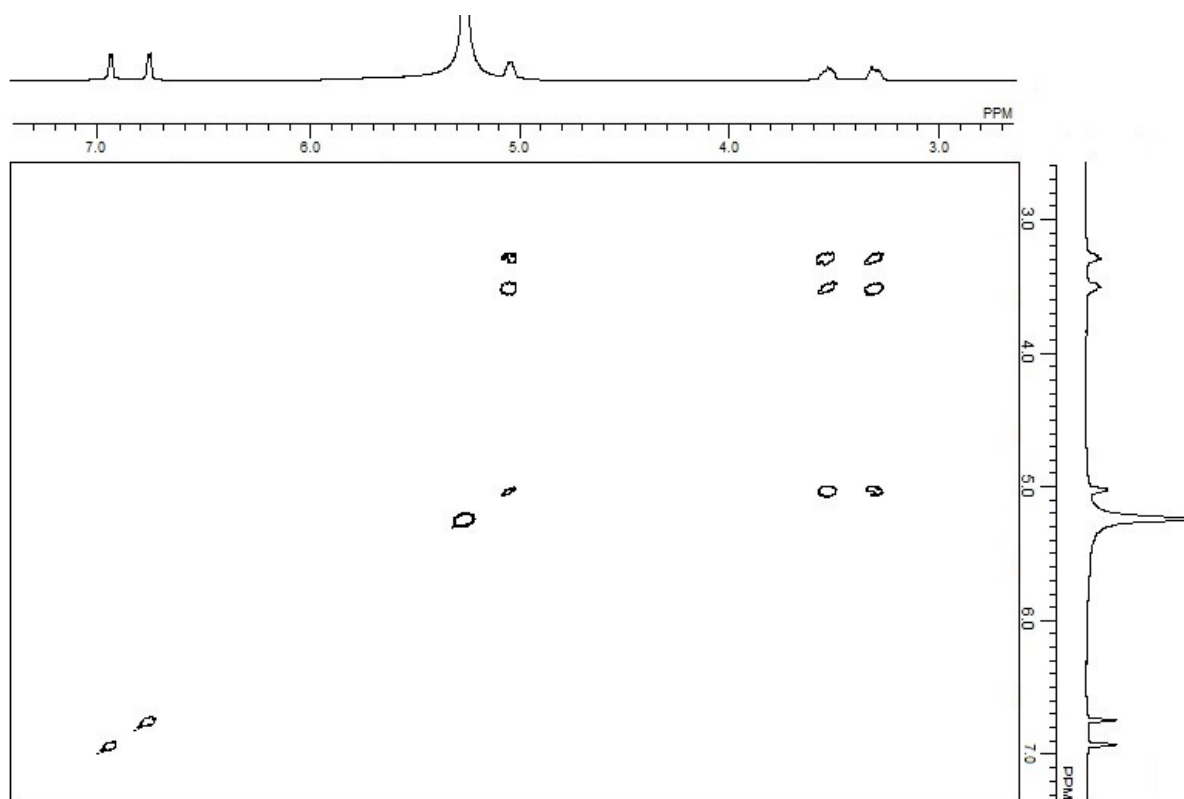
¹H-NMR (270 MHz, D₂O)



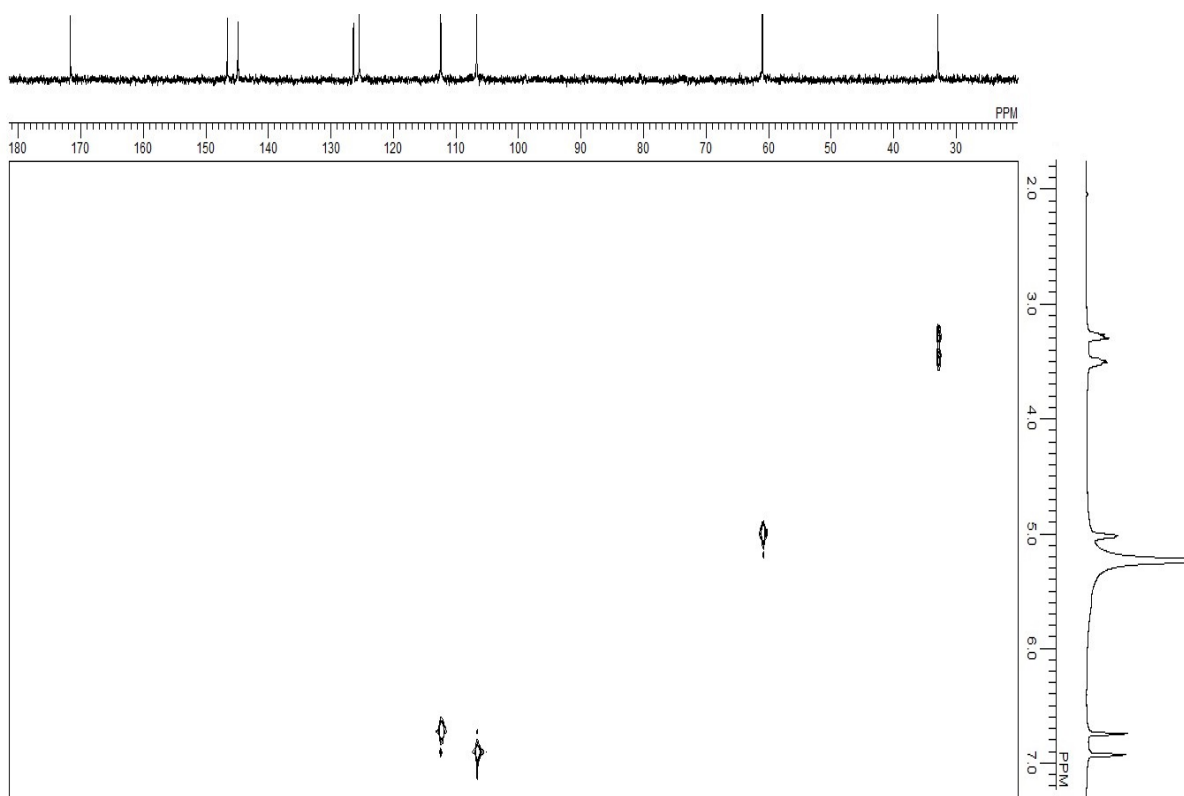
¹³C-NMR (67.5 MHz, D₂O)



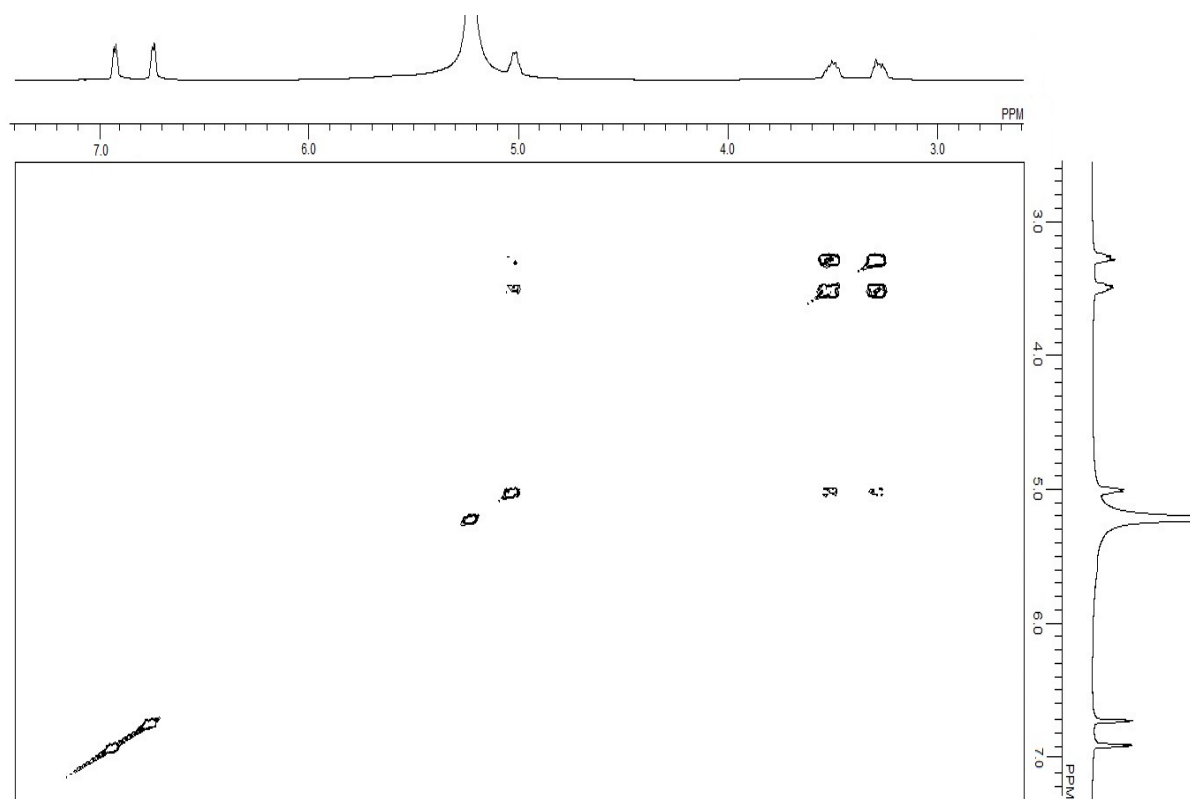
^1H - ^1H COSY (500 MHz, D_2O)



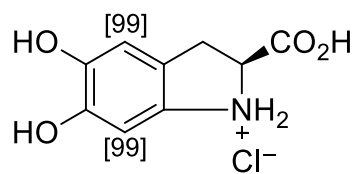
^{13}C - ^1H HETCOR (500 MHz, D_2O)



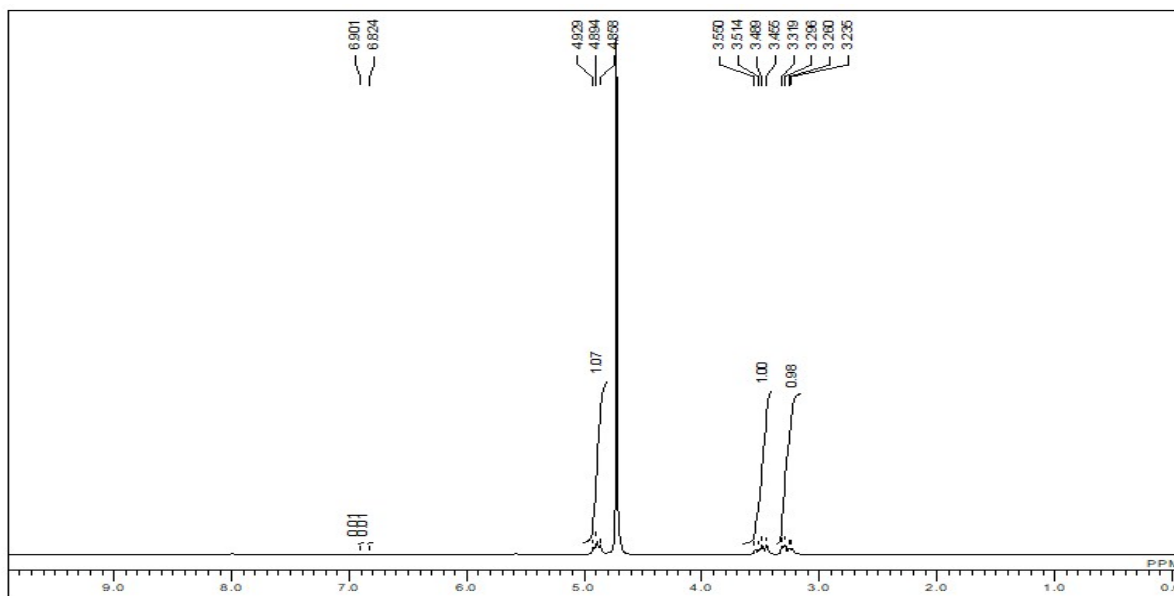
^1H - ^1H TOCSY (500 MHz, D_2O)



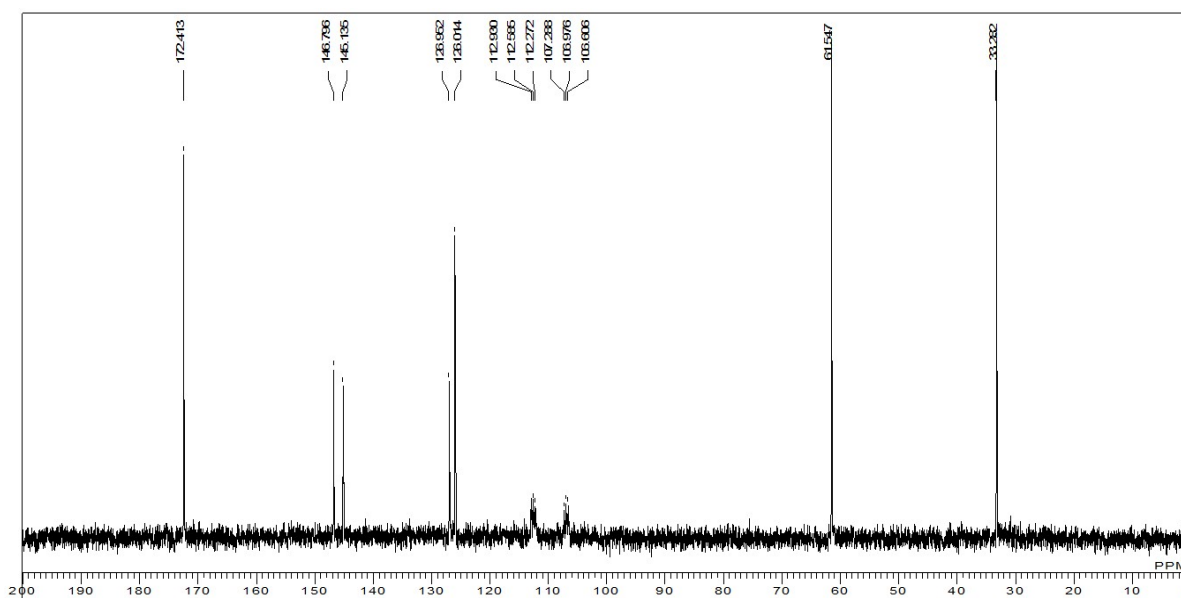
cycloDOPA-4,7-d₂ (4)



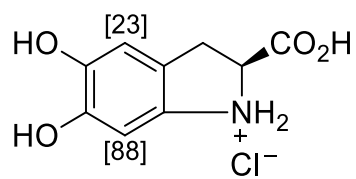
¹H-NMR (270 MHz, D₂O)



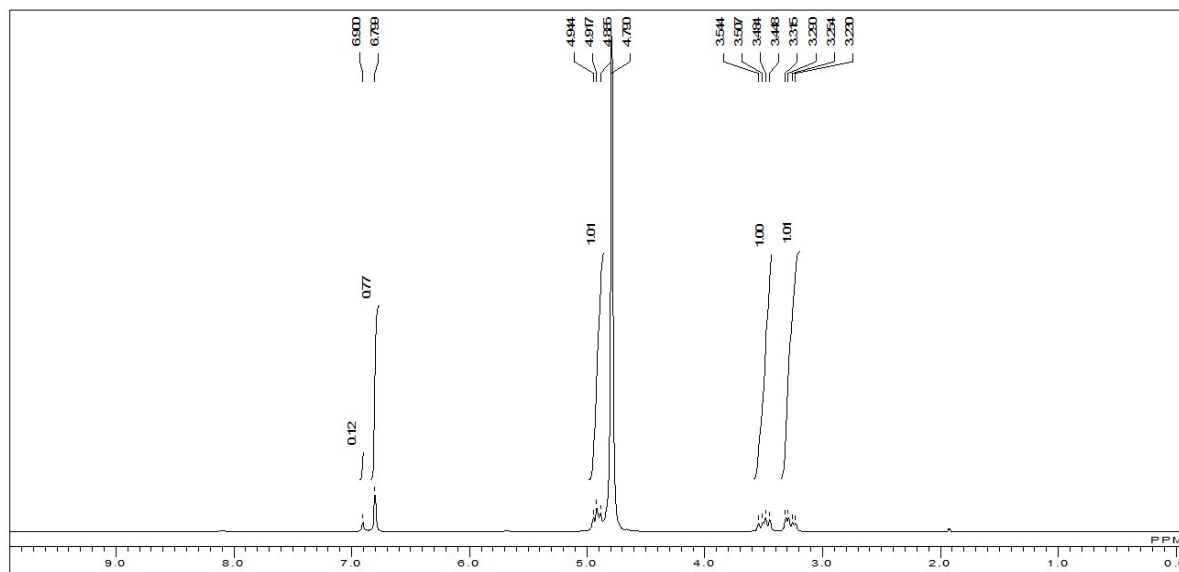
¹³C-NMR (67.5 MHz, D₂O)



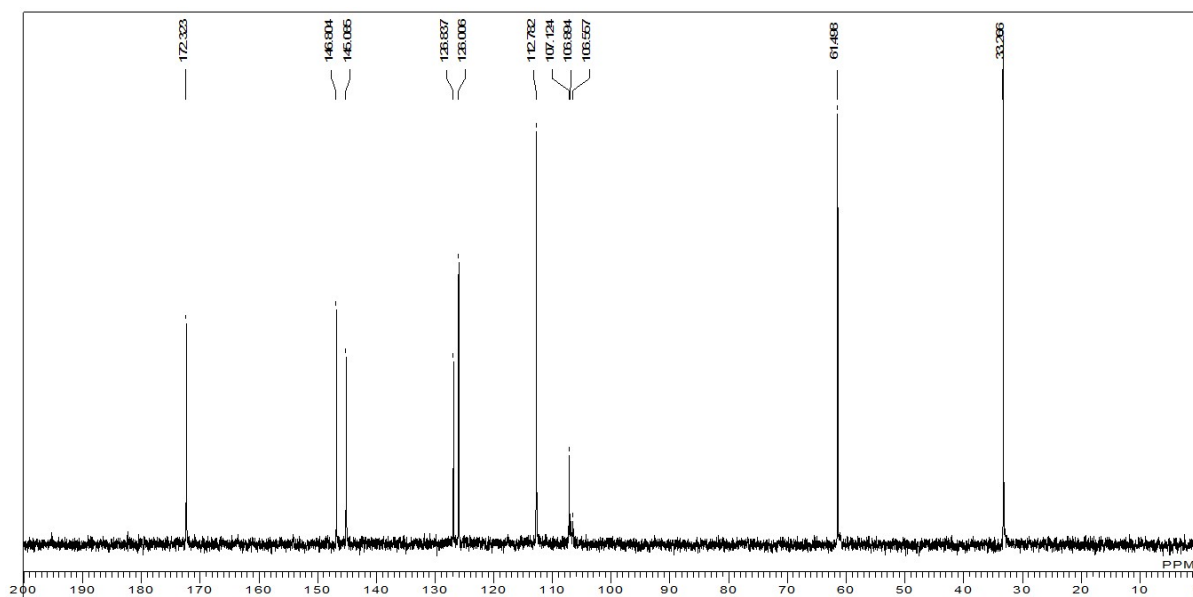
cycloDOPA-7-d (5)



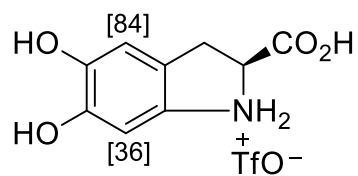
¹H-NMR (270 MHz, D₂O)



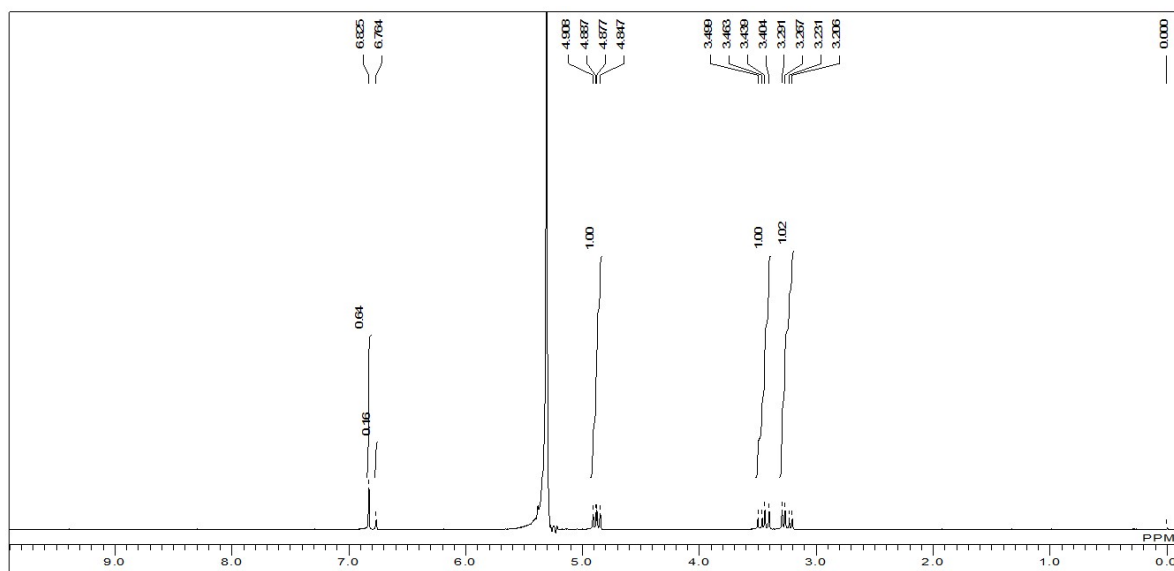
¹³C-NMR (67.5 MHz, D₂O)



cycloDOPA-4-*d* (7)



¹H-NMR (270 MHz, D₂O)



¹³C-NMR (67.5 MHz, D₂O)

