



SUPPLEMENTARY MATERIAL TO
**Synthesis and biological activity of hydroxycinnamoyl-
-containing antiviral drugs**

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ANALYTIC AND SPECTRAL DATA FOR THE SYNTHESIZED COMPOUNDS

N-[(*E*)-3-(3',4'-Dihydroxyphenyl)-2-propenoyl]oseltamivir (**1**). Yield: 48 %; Anal. Calcd. for C₂₅H₃₄N₂O₇: C, 63.27; H 7.22; N, 5.90 %. Found: C, 63.31; H, 7.18; N, 5.89 %; ¹H-NMR (400.15 MHz, CDCl₃, δ / ppm): 0.82 (3H, *t*, *J* = 7.3 Hz, -CHCH₂CH₃), 0.87 (3H, *t*, *J* = 7.3 Hz, -CHCH₂CH₃), 1.26 (3H, *t*, *J* = 7.3 Hz, -O-CH₂CH₃), 1.49 (4H, *q*, *J* = 7.3 Hz, 2 × -CHCH₂CH₃), 1.84 (3H, *s*, -C(O)CH₃), 2.73 (1H, *m*, -CHCH₂CH_{2a}), 2.78 (1H, *m*, -CHCH₂CH_{2b}), 3.35 (1H, *m*, -CHCH₂CH₃), 4.15–4.17 (3H, *m*, 2 × -O-CH₂CH₃ + 1 × -CHCH₂CH₂), 4.31 (1H, *brs*, -CHCH₂CH₂), 6.19 (1H, *d*, *J* = 15.5 Hz, =CH-C(O)-), 6.68 (2H, *s*, 2 × *o*-CH), 6.75 (1H, *brs*, =CH), 6.97 (1H, *s*, *m*-CH), 7.32 (2H, *brs*, 2 × NH), 7.38 (1H, *d*, *J* = 15.5 Hz, =CH-Ph), 8.18 (2H, *brs*, 2 × OH); ¹³C-NMR (100.62 MHz, CDCl₃, δ / ppm): 172.9 (COOC₂H₅), 167.8 (HNCO), 166.3, 146.9, 144.8, 142.1 (=CH-Ph), 137.7 (=CHCHCH), 129.2 (C_q), 127.1 (C_q), 121.9 (*o*-CH), 117.3 (=CH-CO), 116.0 (*o*-CH), 114.8 (CH), 82.8 (-O-CHCH₂CH₃), 75.8 (-OCH), 61.0 (-O-CH₂CH₃), 55.3 (-C(O)HN-CH), 48.4 (-HN-CH), 30.6 (-CHCH₂CH₂), 26.4 (-CHCH₂CH₃), 25.8 (-CHCH₂CH₃), 22.9 (-O)CCH₃, 14.2 (-O-CH₂CH₃), 9.5 (-CHCH₂CH₃), 9.5 (-CHCH₂CH₃); ESI-MS (*m/z*): 475 ([M+H]⁺), 497 ([M+Na]⁺), 949 ([2M+H]⁺); UV-Vis (EtOH) (λ_{max} / nm (ε / L mol⁻¹ cm⁻¹): 203 (32490), 218 (30971), 297 (17434), 325 (20457).

N-[(*E*)-3-(3',5'-Dimethoxy-4'-hydroxyphenyl)-2-propenoyl]oseltamivir (**2**). Yield: 42 %; Anal. Calcd. for C₂₇H₃₈N₂O₈: C, 62.53; H 7.39; N, 5.40 %. Found: C, 62.47; H, 7.41; N, 5.67 %; ¹H-NMR (400.15 MHz, CDCl₃, δ / ppm): 0.92 (3H, *t*, *J* = 7.2 Hz, -CHCH₂CH₃), 0.90 (3H, *t*, *J* = 7.2 Hz, -CHCH₂CH₃), 1.29

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(3H, *t*, $J = 7.2$ Hz, $-\text{O}-\text{CH}_2\text{CH}_3$), 1.53 (4H, *q*, $J = 7.2$ Hz, $2\times-\text{CHCH}_2\text{CH}_3$), 1.96 (3H, *s*, $-\text{C}(\text{O})\text{CH}_3$), 2.37 (1H, *dd*, $J = 16.8, 9.6$ Hz, $-\text{CHCHCH}_2\text{a}$), 2.86 (1H, *dd*, $J = 16.8, 5.6$ Hz, $-\text{CHCHCH}_2\text{b}$), 3.41 (1H, *m*, $-\text{CHCH}_2\text{CH}_3$), 3.88 (6H, *s*, $2\times\text{OCH}_3$), 4.05-4.40 (5H, *m*, $-\text{O}-\text{CH}_2\text{CH}_3$, $-\text{CHCHCH}_2$, $-\text{CHCHCH}_2$, $-\text{CHCHCHCH}_2$), 5.82 (1H, *s*, OH), 6.18 (1H, *d*, $J = 8.3$ Hz, NH), 6.25 (1H, *d*, $J = 15.1$ Hz, $=\text{CH}-\text{C}(\text{O})-$), 6.71 (2H, *s*, $2\times\text{o}-\text{CH}$), 6.75 (1H, *d*, $J = 9.6$ Hz, NH), 6.82 (1H, *brs*, $=\text{CH}$), 7.48 (1H, *d*, $J = 15.1$ Hz, $=\text{CH}-\text{Ph}$); ^{13}C -NMR (100.62 MHz, CDCl_3 , δ / ppm): 172.9 (COOC_2H_5), 167.8 (HNCO), 166.3, 147.2, 146.6, 141.7 ($=\text{CH}-\text{Ph}$), 137.4 ($=\text{CHCHCH}$), 136.7 (Cq), 129.5 (Cq), 126.0 (Cq), 118.2 ($=\text{CH}-\text{CO}$), 104.8 ($2\times\text{o}-\text{CH}$), 82.8 ($-\text{O}-\text{CHCH}_2\text{CH}_3$), 75.6 ($-\text{OCH}$), 61.0 ($-\text{O}-\text{CH}_2$), 56.2 ($2\times\text{OCH}_3$), 54.5 ($-\text{C}(\text{O})\text{HN}-\text{CH}$), 48.8 ($-\text{HN}-\text{CH}$), 30.9 ($-\text{CHCHCH}_2$), 26.3 ($-\text{CHCH}_2\text{CH}_3$), 25.8 ($-\text{CHCH}_2\text{CH}_3$), 23.3 ($-(\text{O})\text{CCH}_3$), 14.2 ($-\text{O}-\text{CH}_2\text{CH}_3$), 9.5 ($-\text{CHCH}_2\text{CH}_3$), 9.2 ($-\text{CHCH}_2\text{CH}_3$); ESI-MS (m/z): 519.2 ($[\text{M}+\text{H}]^+$), 541 ($[\text{M}+\text{Na}]^+$); UV-Vis (EtOH) (λ_{max} / nm (ϵ / $\text{L mol}^{-1}\text{cm}^{-1}$): 203 (56915), 225 (42016), 323 (24306).

N-[(E)-3-(3'-Methoxy-4'-hydroxyphenyl)-2-propenoyl]oseltamivir (**3**). Yield: 31.4 %; Anal. Calcd. for $\text{C}_{26}\text{H}_{36}\text{N}_2\text{O}_7$: C, 63.92; H 7.43; N, 5.40 %. Found: C, 63.84; H, 7.39; N, 5.36 %; ^1H -NMR (400.15 MHz, CDCl_3 , δ / ppm): 0.89 (3H, *t*, $J = 7.5$ Hz, $-\text{CHCH}_2\text{CH}_3$), 0.92 (3H, *t*, $J = 7.5$ Hz, $-\text{CHCH}_2\text{CH}_3$), 1.29 (3H, *t*, $J = 7.5$ Hz, $-\text{O}-\text{CH}_2\text{CH}_3$), 1.53 (4H, *q*, $J = 7.5$ Hz, $2\times-\text{CHCH}_2\text{CH}_3$), 1.94 (3H, *s*, $-\text{C}(\text{O})\text{CH}_3$), 2.37 (1H, *dd*, $J = 18.0, 9.7$ Hz, $-\text{CHCHCH}_2\text{a}$), 2.86 (1H, *dd*, $J = 18.0, 5.3$ Hz, $-\text{CHCHCH}_2\text{b}$), 3.41 (1H, *m*, $-\text{CHCH}_2\text{CH}_3$), 3.87 (3H, *s*, OCH_3), 4.05-4.40 (5H, *m*, $-\text{O}-\text{CH}_2\text{CH}_3$, CHCHCH_2 , $-\text{CHCHCH}_2$, $-\text{CHCHCHCH}_2$), 6.10 (1H, *brs*, OH), 6.24 (1H, *d*, $J = 15.3$ Hz, $=\text{CH}-\text{C}(\text{O})-$), 6.30 (1H, *d*, $J = 8.5$ Hz, NH), 6.80 (2H, NH + $=\text{CH}$), 6.85 (1H, *d*, $J = 7.7$ Hz, *m*-CH), 6.95 (1H, *d*, $J = 2.0$ Hz, *o*-CH), 6.99 (1H, *dd*, $J = 7.7, 2.0$ Hz, *o*-CH), 7.50 (1H, *d*, $J = 15.3$ Hz, $=\text{CH}-\text{Ph}$); ^{13}C -NMR (100.62 MHz, CDCl_3 , δ / ppm): 171.8 (COOC_2H_5), 166.7 (HNCO), 165.9, 147.2, 146.6, 141.4 ($=\text{CH}-\text{Ph}$), 137.5 ($=\text{CHCHCH}$), 129.4 (Cq), 127.1 (Cq), 122.5 (*o*-CH), 117.9 ($=\text{CH}-\text{CO}$), 114.7 (*m*-CH), 109.2 (*o*-CH), 82.8 ($-\text{O}-\text{CHCH}_2\text{CH}_3$), 75.7 ($-\text{OCH}$), 61.0 ($-\text{O}-\text{CH}_2\text{CH}_3$), 55.9 (OCH_3), 54.5 ($-\text{C}(\text{O})\text{HN}-\text{CH}$), 48.8 ($-\text{HN}-\text{CH}$), 30.8 ($-\text{CHCHCH}_2$), 26.3 ($-\text{CHCH}_2\text{CH}_3$), 25.7 ($-\text{CHCH}_2\text{CH}_3$), 23.3 ($-(\text{O})\text{CCH}_3$), 14.2 ($-\text{O}-\text{CH}_2\text{CH}_3$), 9.5 ($-\text{CHCH}_2\text{CH}_3$), 9.2 ($-\text{CHCH}_2\text{CH}_3$); ESI-MS (m/z): 489.5 ($[\text{M}+\text{H}]^+$), 511 ($[\text{M}+\text{Na}]^+$), 977 ($[\text{2M}+\text{H}]^+$); UV-Vis (EtOH) (λ_{max} / nm (ϵ / $\text{L mol}^{-1}\text{cm}^{-1}$): 203 (48276), 218 (45018), 295 (25826), 322 (33300).

N-[(E)-3-(3',4'-Dihydroxyphenyl)-2-propenoyl]rimantadine (**4**). Yield: 68.1 %; Anal. Calcd. for $\text{C}_{21}\text{H}_{27}\text{NO}_3$: C, 73.87; H 7.97; N, 4.10 %. Found: C, 73.64; H, 7.91; N, 4.12 %; ^1H -NMR (400.15 MHz, $\text{DMSO}-d_6$, δ / ppm): 1.08 (3H, *d*, $J = 7.0$ Hz, CH_3), 1.4-1.9 (12H, *m*, $6\times-\text{CH}_2$), 1.98 (3H, CH, cyclo), 3.83 (1H, *m*, $-\text{CHCH}_3$), 5.67 (1H, *d*, $J = 10.0$ Hz, NH), 6.25 (1H, *d*, $J = 15.8$ Hz, $=\text{CH}$), 6.76 (1H, *brs*, OH), 6.86 (1H, *d*, $J = 8.2$ Hz, *m*-CH), 6.96 (1H, *dd*, $J = 8.2$ Hz, 1.8 Hz,

o-CH), 7.18 (1H, *d*, *J* = 1.8 Hz, *o*-CH), 7.55 (1H, *d*, *J* = 15.8 Hz, =CH), 8.15 (1H, *s*, OH); ¹³C-NMR (100.62 MHz, DMSO-*d*₆, δ / ppm): 166.9 (CO), 146.8, 144.3, 142.3 (CH), 127.0 (Cq), 120.3 (*o*-CH), 117.5 (=CH), 115.8 (*o*-CH), 115.4 (*m*-CH), 53.7 (CHCH₃), 38.4 (CH₂, cycle), 37.0 (CH₂, cycle), 28.2 (CH, cycle), 14.5(CHCH₃); ESI-MS (*m/z*): 342.1 ([M+H]⁺), 364.5 ([M+Na]⁺); UV-Vis (EtOH) (λ_{max}/ nm (ε/ L mol⁻¹cm⁻¹)): 220 (61680), 242 (52404), 296 (54191), 322 (58566).

N-[(*E*)-3-(3',5'-Dimethoxy-4'-hydroxyphenyl)-2-propenoyl]amantadine (**5**). Yield: 53 %; Anal. Calcd. for C₂₁H₂₇NO₄: C, 70.56; H 7.61; N, 3.92 %. Found: C, 70.58; H, 7.47; N, 3.96 %; ¹H-NMR (400.15 MHz, DMSO-*d*₆, δ / ppm): 1.62 (6H, *s*, cycle), 1.9–2.1 (9H, *m*, cycle), 3.86 (6H, *s*, 2×OCH₃), 5.70 (1H, *s*, NH), 6.51 (1H, *d*, *J* = 15.6 Hz, HC=), 6.86 (2H, *s*, Ar-H(_o)), 7.24 (1H, *d*, *J* = 15.6 Hz, HC=), 9.80 (1H, *s*, OH); ¹³C-NMR (100.62 MHz, DMSO-*d*₆, δ / ppm): 165.9 (CO), 148.1, 153.4 (ArOH), 141.2 (=CH-Ar), 127.0 (Cq-Ar), 122.2 (HN-CH=), 115.3 (=CH), 105.3 (2×Ar-*ortho*-CH), 57.2 (OCH₃), 53.1 (HN-CH), 50.9 (Cq, cycle), 42.6 (CH₂, cycle), 37.3 (CH₂), 30.4 (CH, cycle); ESI-MS (*m/z*): 358 ([M+H]⁺), 380 ([M+Na]⁺), 715 ([2M+H]⁺), 737.1 ([2M+Na]⁺); UV-Vis (EtOH) (λ_{max} / nm (ε / L mol⁻¹ cm⁻¹)): 201 (32395), 235 (34457), 320 (30539).

N-[(*E*)-3-(3'-methoxy-4'-hydroxyphenyl)-2-propenoyl]amantadine (**6**). Yield: 42.1 %; Anal. Calcd. for C₂₀H₂₅NO₃: C, 73.37; H 7.70; N, 4.28 %. Found: C, 73.41; H, 7.73; N, 4.56 %; ¹H-NMR (400.15 MHz, DMSO-*d*₆, δ / ppm): 1.49 (6H, *s*, cycle), 1.93–2.30 (9H, cycle), 3.82 (3H, *s*, OCH₃), 6.46 (1H, *d*, *J* = 15.5 Hz, HC=), 6.82 (1H, *d*, *J* = 8.1 Hz, Ar-H(*m*)), 7.12 (1H, *d*, *J* = 1.8 Hz, Ar-H(*o*)), 7.28 (1H, *s*, Ar-H(*o*)), 7.31 (1H, *s*, NH), 7.52 (1H, *d*, *J* = 15.5 Hz, HC=), 9.02 (1H, *s*, OH); ¹³C-NMR (100.62 MHz, DMSO-*d*₆, δ / ppm): 166.1(CO), 152.6, 141.0 (=CH), 129.1 (2C, Ar-CH), 126.1 (Cq), 120.2 (=CH), 115.7 (2C, Ar-CH), 56.3 (OCH₃), 53.3 (HN-CH), 42.6 (CH₂, cycle), 37.3 (CH₂), 30.4 (CH, cycle); ESI-MS (*m/z*): 328 ([M+H]⁺), 350 ([M+Na]⁺), 390 ([M+Na+K]⁺); UV-Vis (EtOH) (λ_{max} / nm (ε / L mol⁻¹ cm⁻¹)): 218 (97221), 234 (91575), 293 (102106), 321 (120575).

N-[(*E*)-3-(4'-hydroxyphenyl)-2-propenoyl]amantadine (**7**). Yield: 40 %; Anal. Calcd. for C₁₉H₂₃NO₂: C, 76.74; H 7.80; N, 4.71 %. Found: C, 76.71; H, 7.84; N, 4.49 %; ¹H-NMR (400.15 MHz, DMSO-*d*₆, δ / ppm): 1.62 (6H, *s*, cycle), 1.9–2.1 (9H, *m*, cycle), 6.43 (1H, *d*, *J* = 15.6 Hz, HC=), 6.76 (2H, *d*, *J* = 8.38 Hz, *p*-H), 7.19 (1H, *d*, *J* = 15.6 Hz, HC=), 7.32 (2H, *d*, *J* = 8.38 Hz, *o*-H), 7.42 (1H, *s*, NH), 9.80 (1H, *s*, OH); ¹³C-NMR (100.62 MHz, DMSO-*d*₆, δ / ppm): 164.6 (CO), 158.6, 138.0 (=CH), 129.1 (2C, Ar-CH), 126.1 (Cq), 120.2 (=CH), 115.7 (2C, Ar-CH), 50.9 (Cq, cycle), 41.3 (CH₂, cycle), 35.9 (CH₂), 28.9 (CH, cycle); ESI-MS (*m/z*): 298 ([M+H]⁺), 320 ([M+Na]⁺); UV-Vis (EtOH) (λ_{max} / nm): 212 (30565), 224 (25452), 293 (20254).