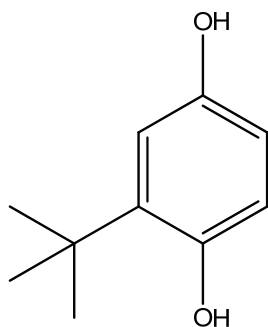


SUPPLEMENTARY MATERIAL TO
Alkylamino and aralkylamino derivatives of avarone and its mimetic as selective agents against non-small cell lung cancer cells, their antibacterial and antifungal potential

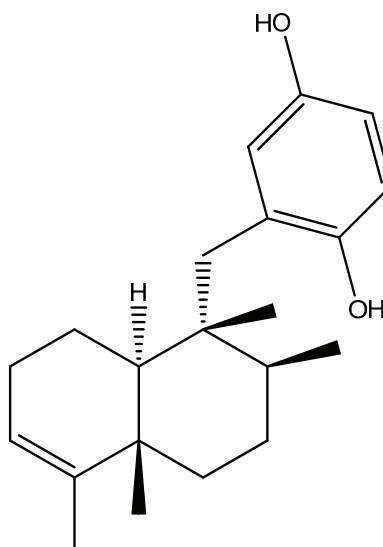
MARKO JEREMIĆ^{1#}, JELENA DINIĆ², MILICA PEŠIĆ², MARIJA STEPANOVIĆ²,
IRENA NOVAKOVIĆ^{3#}, DEJAN ŠEGAN⁴ and DUŠAN SLADIĆ^{4##*}

¹Innovation Center of Faculty of Chemistry, University of Belgrade, Studentski trg 12–16, 11000 Belgrade, Serbia, ²Institute for Biological Research „Siniša Stanković“, University of Belgrade, Despota Stefana 142, 11060 Belgrade, Serbia, ³Institute of Chemistry, Technology and Metallurgy, University of Belgrade, Center for Chemistry, Njegoševa 12, 11000 Belgrade, Serbia and ⁴Faculty of Chemistry, University of Belgrade, Studentski trg 12–16, 11000 Belgrade, Serbia

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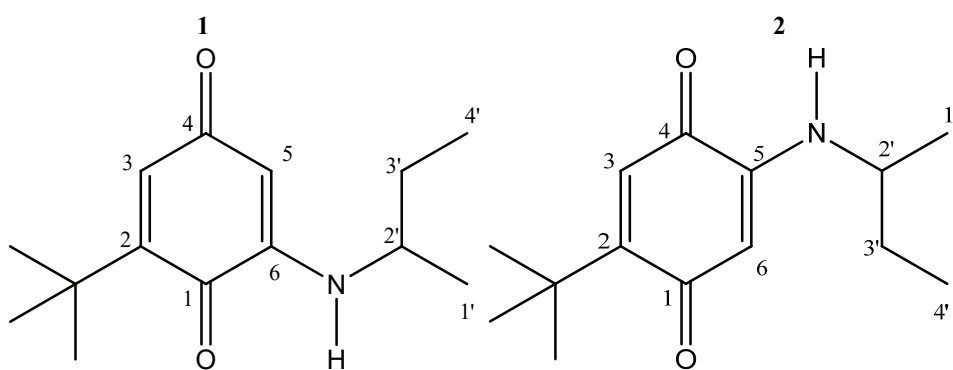
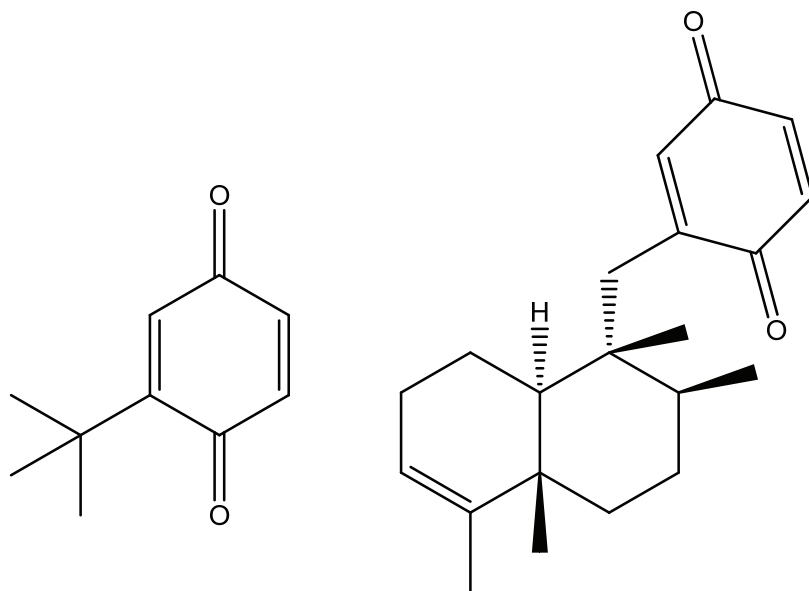


tert-butylhydroquinone



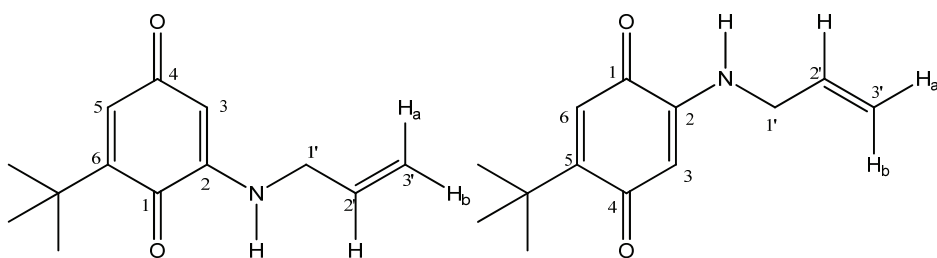
avarol

* Corresponding author. E-mail: dsladic@chem.bg.ac.rs



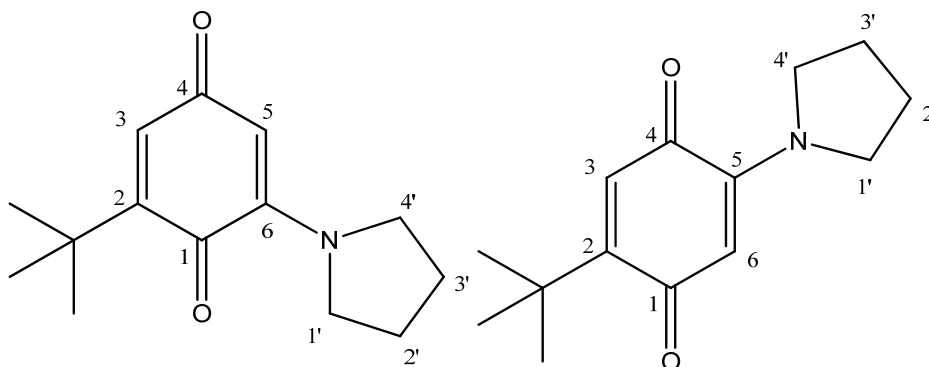
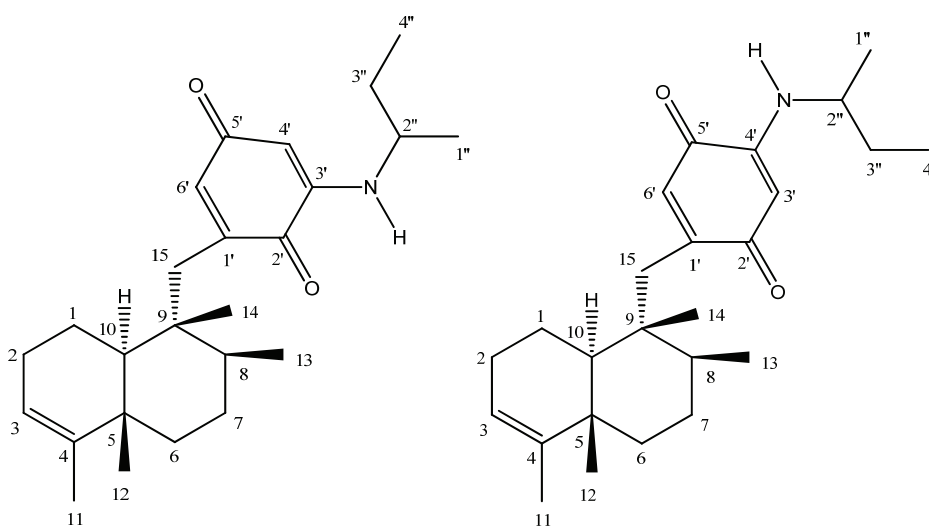
3a

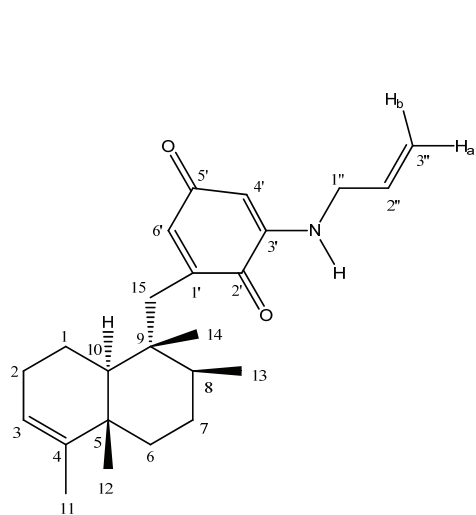
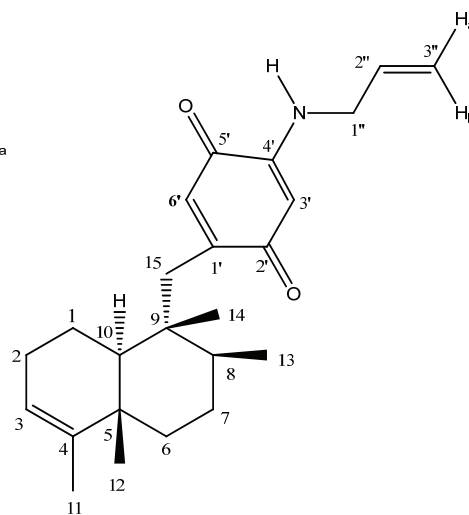
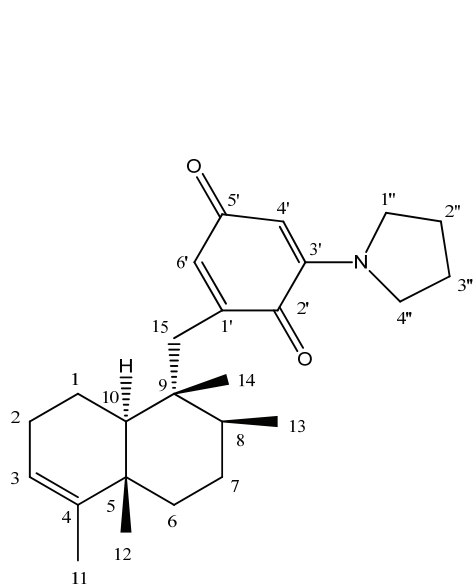
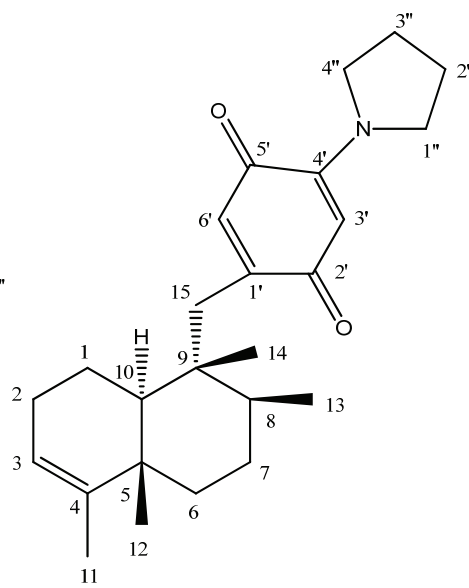
3b

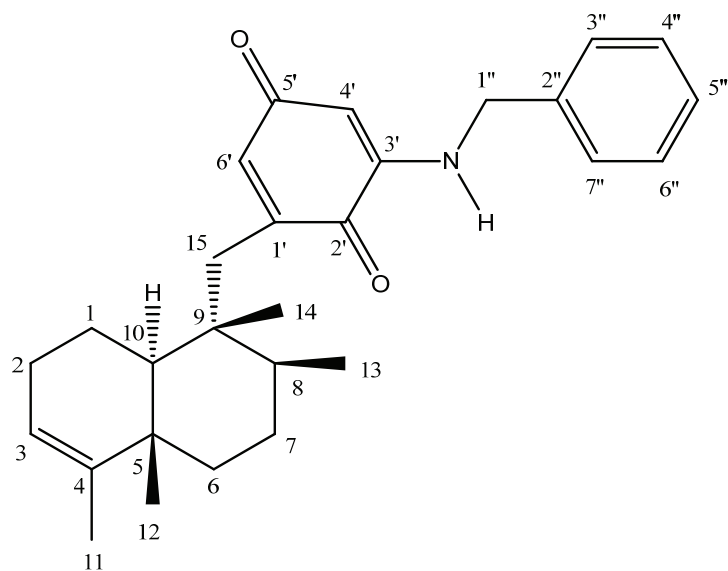
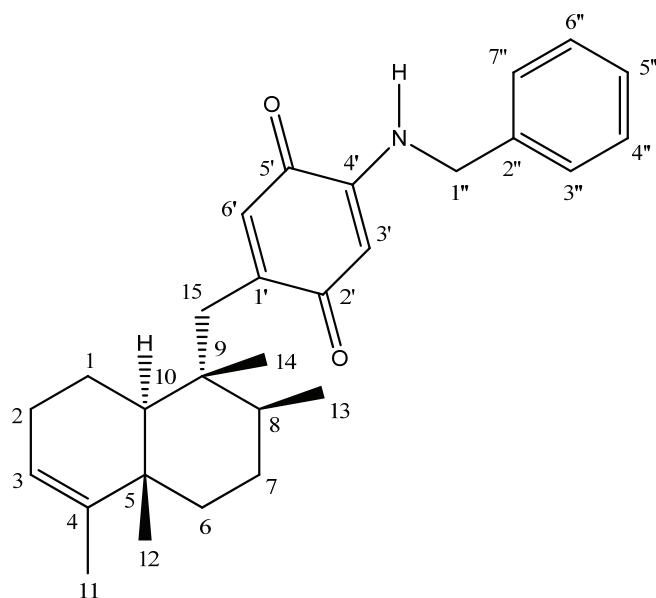


4a

4b

**5a****5b****7a****7b**

**8a****8b****9a****9b**

**10a****10b**

Scheme S-1. Structures of the derivatives.

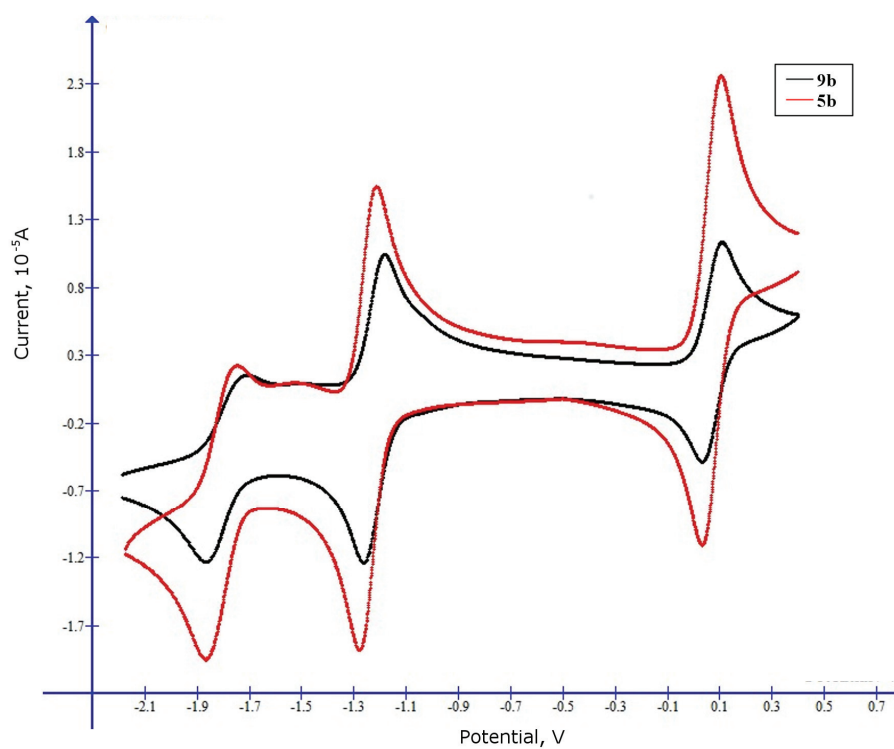


Fig. S-1. Cyclic voltammogram of compounds **5b** and **9b**.

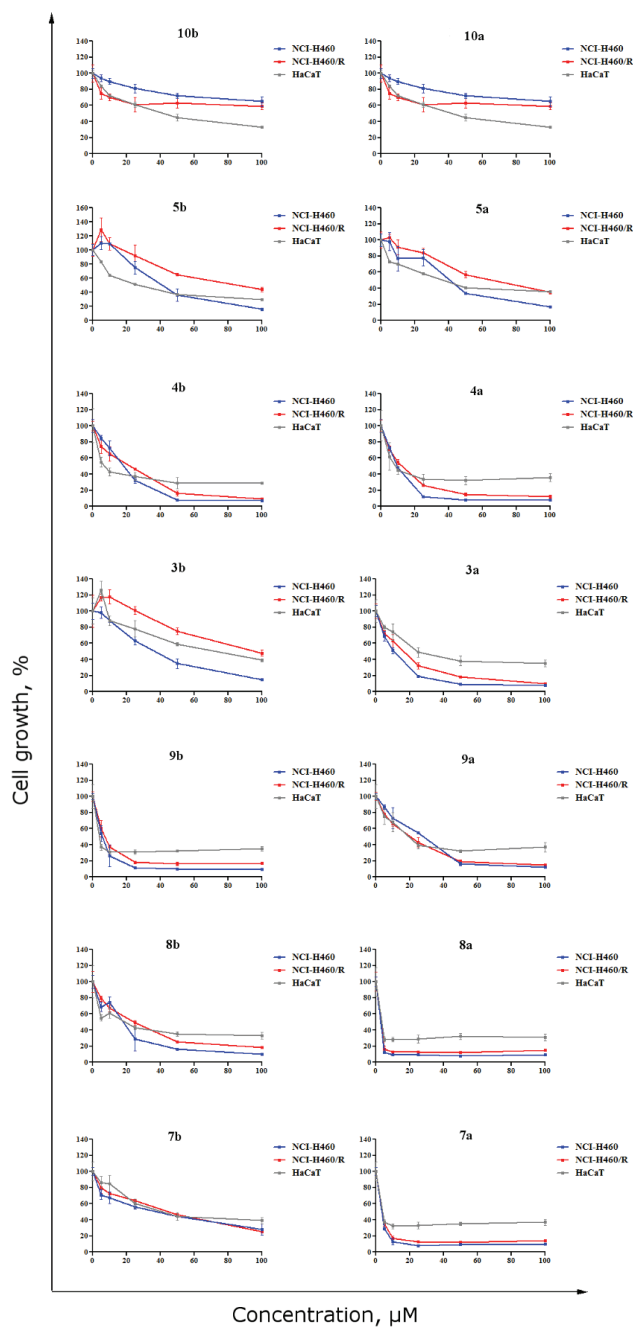


Fig. S-2. Cell growth inhibition by TBQ and avarone derivatives. Inhibitory potential of 14 compounds was studied in NCI-H460, NCI-H460/R and HaCaT cells after 72 h by the MTT assay.

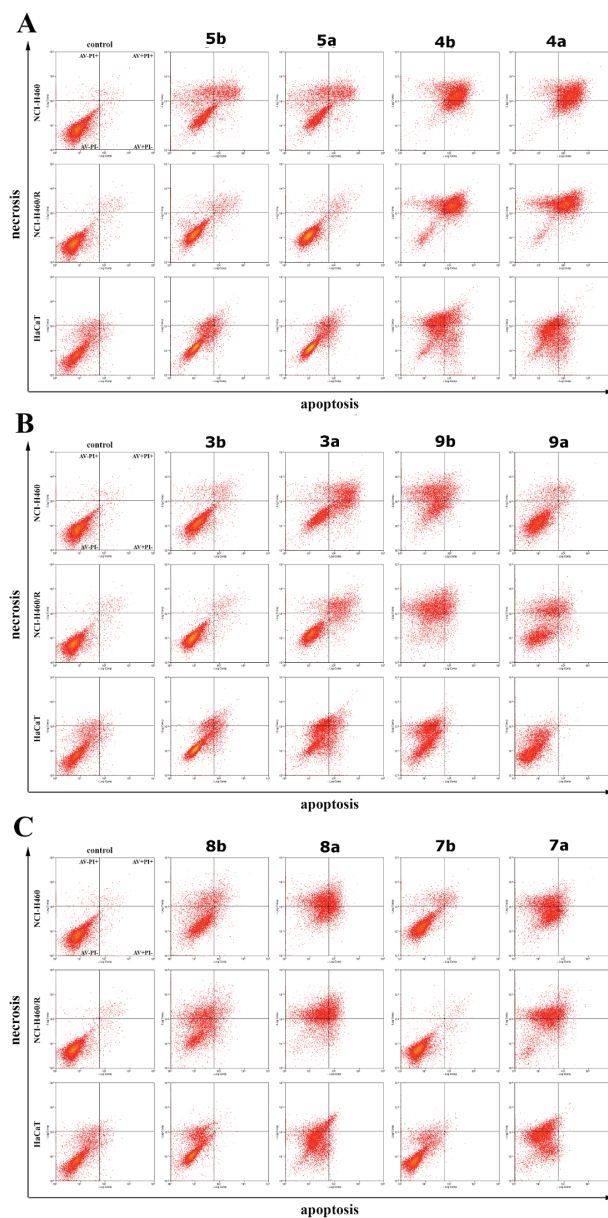


Fig. S-3. Cell death induction by TBQ and avarone derivatives. Cell death type was investigated in NCI-H460, NCI-H460/R and HaCaT cells after 72 h by flow cytometry (AV/PI staining). (A) Treatment with 25 μ M **5b**, **5a**, **4b** and **4a**. (B) Treatment with 25 μ M **3b**, **3a**, **9b** and **9a**. (C) Treatment with 25 μ M **8b**, **8a**, **7b** and **7a**. The assay distinguishes viable cells (AV-PI-), early apoptotic cells (AV+PI-), late apoptotic cells (AV+PI+) and necrotic cells (AV-PI+). The *x*-axis represents the green FL1-H channel and the *y*-axis represents the red FL2-H channel.

2-tert-Butyl-6-(sec-butylamino)cyclohexa-2,5-diene-1,4-dione (3a). The compound was separated from its regioisomer by column chromatography using toluene:ethyl acetate (9:1) as eluent (R_f : 0.46) and purified by preparative thin-layer chromatography using *n*-hexane:acetone (9:1) as eluent (R_f : 0.36).

Yield: 139.2 mg, 32.4 %; reddish brown oil; IR (ATR, cm^{-1}): 3379, 3288, 2966, 2874, 1670, 1633, 1586, 1508, 1457, 1344, 1264, 1171, 1009, 906, 808; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 6.46 (1H, *d*, $J = 2$ Hz, C3-H), 5.58 (1H, *d*, $J = 6$ Hz, C6-NH), 5.42 (1H, *d*, $J = 2$ Hz, C5-H), 3.29 (1H, *m*, C2'-H), 1.57 (2H, *m*, C3'-H₂), 1.27 (9H, *s*, C2-C(CH₃)₃), 1.12 (3H, *d*, $J = 6$ Hz, C1'-H₃), 0.95 (3H, *t*, $J = 7-8$ Hz, C4'-H₃); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 186.0 (C4), 183.4 (C1), 151.2 (C2), 146.7 (C6), 135.1 (C3), 97.0 (C5), 49.6 (C2'), 34.7 (C2-C(CH₃)₃), 29.0 (3C, C2-C(CH₃)₃), 28.7 (C3'), 19.0 (C1'), 10.2 (C4'); (+)ESI-HRMS (m/z) calcd. for [C₁₄H₂₁NO₂+H⁺]: 236.16451. Found: 236.16441; calcd. for [C₁₄H₂₁NO₂+K⁺] 274.12039. Found: 274.12284; UV-Vis (MeOH, *c*: 0.083 mg mL⁻¹, λ_{max} / nm, (ϵ / dm² mol⁻¹)): 274 (6.61×10⁴), 486 (2.63×10⁴); E_{c1} : -1.210 V, E_{a1} : -1.126 V, E_{c2} : -1.890 V, E_{a2} : -1.741 V, E°_1 / Fc : -1.170 V.

2-tert-Butyl-5-(sec-butylamino)cyclohexa-2,5-diene-1,4-dione (3b). The compound was separated from its regioisomer by column chromatography using toluene:ethyl acetate (9:1) as eluent (R_f : 0.70) and purified by preparative thin-layer chromatography using hexane:acetone (9:1) as eluent (R_f : 0.53).

Yield: 41.2 mg, 9.6 %; reddish brown oil; IR (ATR, cm^{-1}): 3379, 3348, 2965, 2875, 1670, 1627, 1588, 1515, 1484, 1457, 1387, 1344, 1223, 1189, 1047, 1017, 895, 834; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 6.43 (1H, *s*, C3-H), 5.38 (1H, *s*, C6-H), 5.28 (1H, *bs*, C5-NH), 3.28 (1H, *m*, C2'-H), 1.57 (2H, *m*, C3'-H₂), 1.30 (9H, *s*, C2-C(CH₃)₃), 1.19 (3H, *d*, $J = 6$ Hz, C1'-H₃), 0.93 (3H, *t*, $J = 8$ Hz, C4'-H₃); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 185.9 (C1), 185.0 (C4), 160.0 (C2), 144.5 (C5), 127.4 (C3), 100.2 (C6), 49.3 (C2'), 35.7 (C2-C(CH₃)₃), 29.6 (3C, C2-C(CH₃)₃), 28.8 (C3'), 19.2 (C1'), 10.2 (C4'); (+)ESI-HRMS (m/z) calcd. for [C₁₄H₂₁NO₂+H⁺]: 236.16451. Found: 236.16475; calcd. for [C₁₄H₂₁NO₂+K⁺] 274.12039. Found: 274.12345; UV-Vis (*c*: 0.083 mg mL⁻¹ in MeOH, λ_{max} / nm (ϵ / dm² mol⁻¹)): 270 (7.86×10⁴), 482 (2.24×10⁴); E_{c1} : -1.218 V, E_{a1} : -1.154 V, E_{c2} : -1.868 V, E_{a2} : -1.744 V, E°_1 / Fc : -1.186 V.

2-(Allylamino)-6-tert-butylcyclohexa-2,5-diene-1,4-dione (4a). The compound was separated from its regioisomer by column chromatography using toluene:ethyl acetate (9:1) as eluent (R_f : 0.35) and purified by preparative thin-layer chromatography using hexane:acetone (8:2) as eluent (R_f : 0.45).

Yield 168 mg, 41.9 %; reddish brown crystals; m.p.: 64 °C; IR (ATR, cm^{-1}): 3285, 3073, 2990, 2961, 2909, 2871, 1673, 1627, 1579, 1499, 1432, 1367, 1339, 1293, 1250, 1204, 1164, 1073, 991, 915, 804, 703, 644; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 6.47 (1H, *d*, $J = 2$ Hz, C5-H), 5.86 (2H, *m*, C2-NH & C2'-H), 5.45 (1H, *d*, $J = 2$ Hz, C3-H), 5.31 (1H, *dd*, $J_1 = 8$ Hz & $J_2 = 1$ Hz, C3'-H_a), 5.24

(1H, *s*, C3'-H_b), 3.75 (2H, *t*, *J* = 6 Hz, C1'-H₂), 1.27 (9H, *s*, C6-C(CH₃)₃); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 186.2 (C4), 183.1 (C1), 151.3 (C6), 147.3 (C2), 134.8 (C2'), 131.7 (C5), 118.1 (C3'), 97.8 (C3), 44.9 (C1'), 34.7 (C6-C(CH₃)₃), 28.9 (3C, C6-C(CH₃)₃); (+)ESI-HRMS (*m/z*) calcd: for [C₁₃H₁₇NO₂+H⁺]: 220.13321. Found: 220.13319; UV-Vis (*c*: 0.083 mg mL⁻¹ in MeOH, λ_{\max} / nm, (ϵ / dm² mol⁻¹)): 272 (6.55×10⁴), 476 (2.33×10⁴). *E*_{c1}: -1.180 V, *E*_{a1}: -1.121 V, *E*_{c2}: -1.812 V, *E*_{a2}: -1.712 V, *E*^o₁ / *Fc*: -1.149 V.

2-(*Allylamino*)-5-*tert-butylcyclohexa-2,5-diene-1,4-dione* (**4b**). The compound was separated from its regioisomer by column chromatography using toluene:ethyl acetate (9:1) as eluent (*R*_f: 0.57) and purified by preparative thin-layer chromatography using hexane:acetone (8:2) as eluent (*R*_f: 0.54).

Yield: 38 mg; 9.5 %; reddish brown crystals; m.p.: 39 °C; IR (ATR, cm⁻¹): 3388, 3067, 3004, 2961, 2916, 2870, 1670, 1627, 1589, 1513, 1456, 1390, 1339, 1248, 1225, 1187, 1017, 992, 930, 896, 837; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 6.45 (1H, *s*, C6-H), 5.84 (1H, *m*, C2'-H), 5.54 (1H, *bs*, C2-NH), 5.41 (1H, *s*, C3-H), 5.28 (1H, *d*, *J* = 6 Hz, C3'-H_a), 5.22 (1H, *s*, C3'-H_b), 3.73 (2H, *t*, *J* = 6 Hz, C1'-H₂), 1.30 (9H, *s*, C5-C(CH₃)₃); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 186.0 (C4), 184.8 (C1), 159.5 (C5), 145.1 (C2), 131.8 (C2'), 127.5 (C6), 118.0 (C3'), 101.1 (C3), 44.7 (C1'), 35.7 (C5-C(CH₃)₃), 29.6 (3C, C5-C(CH₃)₃); (+)ESI-HRMS (*m/z*) calcd for [C₁₃H₁₇NO₂+H⁺]: 220.13321. Found: 220.13311; UV-Vis (*c*: 0.083 mg mL⁻¹ in MeOH, λ_{\max} / nm, (ϵ / dm² mol⁻¹)): 270 (6.52×10⁴), 474 (1.47×10⁴); *E*_{c1}: -1.210 V, *E*_{a1}: -1.152 V, *E*_{c2}: -1.848 V, *E*_{a2}: -1.733 V, *E*^o₁ / *Fc*: -1.181 V.

2-*tert-Butyl-6-(pyrrolidin-1-yl)cyclohexa-2,5-diene-1,4-dione* (**5a**). The compound was separated from its regioisomer by column chromatography using toluene:ethyl acetate (8:2) as eluent (*R*_f: 0.31) and purified by two preparative thin-layer chromatographies, the first using toluene:ethyl acetate (8:2) as the eluent, and then using hexane:acetone (7:3) as the eluent (*R*_f: 0.45).

Yield: 63 mg, 14.8 %; reddish brown crystals; m.p.: 106–107 °C; IR (ATR, cm⁻¹): 2963, 2873, 1670, 1632, 1598, 1563, 1480, 1458, 1413, 1366, 1336, 1314, 1287, 1250, 1174, 1156, 1120, 1049, 999, 907, 796; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 6.45 (1H, *d*, *J* = 2 Hz, C3-H), 5.41 (1H, *d*, *J* = 2 Hz, C5-H), 3.53 (4H, *bs*, C1'-H₂ & C4'-H₂), 1.95 (4H, *m*, C2'-H₂ & C3'-H₂), 1.25 (9H, *s*, C2-C(CH₃)₃); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 185.5 (C4), 185.4 (C1), 151.8 (C2), 149.3 (C6), 133.8 (C3), 101.0 (C5), 50.8 (2C, C1' & C4'), 34.9 (C2-C(CH₃)₃), 29.2 (3C, C2-C(CH₃)₃), 25.1 (2C, C2' and C3'); (+)ESI-HRMS (*m/z*) calcd. for [C₁₄H₁₉NO₂+H⁺]: 234.14886. Found: 234.14892; UV-Vis (*c*: 0.083 mg mL⁻¹ in MeOH, λ_{\max} / nm, (ϵ / dm² mol⁻¹)): 274 (4.80×10⁴), 500 (3.20×10⁴); *E*_{c1}: -1.276 V, *E*_{a1}: -1.214 V, *E*_{c2}: -1.876 V, *E*_{a2}: -1.694 V, *E*^o₁ / *Fc*: -1.244 V.

2-*tert-Butyl-5-(pyrrolidin-1-yl)cyclohexa-2,5-diene-1,4-dione* (**5b**). The compound was separated from its regioisomer by column chromatography using

toluene:ethyl acetate (9:1) as eluent (R_f : 0.49) and purified by preparative thin-layer chromatography using hexane:acetone (7:3) as eluent (R_f : 0.56).

Yield: 48.6 mg, 11.4 %; reddish brown crystals; m.p.: 136 °C; IR (ATR, cm^{-1}): 3360, 3191, 3047, 2956, 2924, 2855, 1739, 1660, 1626, 1582, 1455, 1427, 1370, 1343, 1324, 1260, 1196, 1055, 1019, 930, 899, 838; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 6.31 (1H, *s*, C3-H), 5.38 (1H, *s*, C6-H), 3.51 (4H, *m*, C1'-H₂ & C4'-H₂), 1.93 (4H, *m*, C2'-H₂ & C3'-H₂), 1.28 (9H, *s*, C2-C(CH₃)₃); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 186.3 (C1), 185.1 (C4), 157.8 (C2), 146.2 (C5), 128.5 (C3), 104.2 (C6), 50.2 (2H, C1' & C4'), 35.2 (C2-C(CH₃)₃), 29.5 (3C, C2-C(CH₃)₃), 25.4 (2C, C2' & C3'); (+)ESI-HRMS (m/z) calcd. for [C₁₄H₁₉NO₂+H⁺]: 234.14886. Found: 234.14952; UV-Vis (*c*: 0.083 mg mL⁻¹ in MeOH, λ_{max} / nm, (ϵ / dm² mol⁻¹)): 276 (6.64×10⁴), 502 (3.09×10⁴); E_{c1} : -1.276 V, E_{a1} : -1.214 V, E_{c2} : -1.865 V, E_{a2} : -1.749 V, E°_1 / Fc : -1.243 V.

2-(*sec-Butylamino*)-6-(((1*R*,2*S*,4*aS*,8*aS*)-1,2,4*a*,5-tetramethyl-1,2,3,4,4*a*,7,8,8*a*-octahydronaphthalen-1-yl)methyl)cyclohexa-2,5-diene-1,4-dione (**7a**). The compound was separated from its regioisomer by low-bar chromatography using petroleum ether (b.p. 40–60 °C):ethyl acetate (9:1) as eluent (R_f : 0.26) and purified by preparative thin-layer chromatography using petroleum ether:ethyl acetate (9:1) as eluent.

Yield: 63.9 mg; 17.3 %; reddish brown oil; IR (ATR, cm^{-1}): 3378, 3291, 2962, 2929, 1669, 1634, 1585, 1506, 1453, 1380, 1340, 1288, 1261, 1190, 1149, 1099, 1048, 912, 802, 446; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 6.37 (1H, *d*, J = 2 Hz, C6'-H), 5.52 (1H, *d*, J = 8 Hz, C3'-NH), 5.42 (1H, *d*, J = 2 Hz, C4'-H), 5.14 (1H, *s*, C3-H), 3.28 (1H, *m*, C2''-H), 2.61 (1H, *dd*, J_1 = 2 Hz & J_2 = 14 Hz, C15-H_a), 2.37 (1H, *dd*, J_1 = 4 Hz & J_2 = 14 Hz, C15-H_b), 1.80–2.10 (4H, *m*, C2-H₂ & C6-H₂), 1.10–1.70 (14H, *m*, C1-H₂, C7-H₂, C8-H, C10-H, C11-H₃, C1''-H₃ & C3''-H₂), 0.80–1.10 (12H, *m*, C14-H₃, C13-H₃, C4''-H₃ & C12-H₃); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 185.5 (C5'), 184.1 (C2'), 146.0 (C3'), 144.0 (C4), 142.0 (C1'), 139.8 (C6'), 120.6 (C3), 97.6 (C4'), 49.6 (C2''), 46.7 (C10), 42.0 (C5), 38.4 (C9), 36.6 (C8), 36.0 (C6), 35.0 (C15), 28.7 (C3''), 27.4 (C7), 26.5 (C2), 20.0 (C12), 19.3 (C1), 19.0 (C1''), 18.0 (C11), 17.7 (C14), 16.7 (C13), 10.2 (C4''); (+)ESI-HRMS (m/z) calcd. for [C₂₅H₃₇NO₂+H⁺]: 384.28971. Found: 384.29014; UV-Vis (*c*: 0.083 mg mL⁻¹ in MeOH, λ_{max} / nm, (ϵ / dm² mol⁻¹)): 286 (2.91×10⁴), 492 (1.28×10⁴); E_{c1} : -1.193 V, E_{a1} : -1.127 V, E_{c2} : -1.881 V, E_{a2} : -1.774 V, E°_1 / Fc : -1.158 V; $[\alpha]_{\text{D}}^{20}$ (*c*: 0.083 mg mL⁻¹ in MeOH): -120.

2-(*sec-Butylamino*)-5-(((1*R*,2*S*,4*aS*,8*aS*)-1,2,4*a*,5-tetramethyl-1,2,3,4,4*a*,7,8,8*a*-octahydronaphthalen-1-yl)methyl)cyclohexa-2,5-diene-1,4-dione (**7b**). The compound was separated from its regioisomer by low-bar chromatography using petroleum ether (b.p. 40–60 °C):ethyl acetate (9:1) as eluent (R_f : 0.49) and

purified by preparative thin-layer chromatography using petroleum ether:ethyl acetate (9:1) as eluent.

Yield: 62.2 mg; 16.9 %; reddish brown oil; IR (ATR, cm^{-1}): 3327, 2964, 2927, 1665, 1627, 1587, 1518, 1450, 1380, 1321, 1267, 1215, 1126, 1098, 1032, 999, 978, 898, 846, 792, 696, 636, 463; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 6.36 (1H, *s*, C6'-H), 5.38-5.42 (2H, *m*, C4'-NH & C3'-H), 5.17 (1H, *s*, C3-H), 3.29 (1H, *m*, C2''-H), 2.64 (1H, *dd*, $J_1 = 2$ Hz & $J_2 = 12$ Hz, C15-H_a), 2.48 (1H, *dd*, $J_1 = 2$ Hz & $J_2 = 14$ Hz, C15-H_b), 1.80–2.10 (4H, *m*, C2-H₂ & C6-H₂), 1.10–1.70 (14H, *m*, C1-H₂, C7-H₂, C8-H, C10-H, C11-H₃, C1''-H₃ & C3''-H₂), 0.80–1.10 (12H, *m*, C14-H₃, C13-H₃, C4''-H₃ & C12-H₃); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 185.2 (C2'), 183.8 (C5'), 151.2 (C1'), 145.2 (C4'), 144.0 (C4), 131.8 (C6'), 120.7 (C3), 98.2 (C3'), 49.3 (C2''), 47.1 (C10), 43.1 (C5), 38.5 (C9), 37.0 (C8), 36.0 (C6), 35.6 (C15), 28.7 (C3''), 27.5 (C7), 26.4 (C2), 20.0 (C2), 19.4 (C1), 19.1 (C1''), 18.0 (C11), 17.7 (C14), 16.8 (C13), 10.2 (C4''); (+)ESI-HRMS (*m/z*) calcd. for $[\text{C}_{25}\text{H}_{37}\text{NO}_2+\text{H}^+]$: 384.28971. Found: 384.29020; UV–Vis (*c*: 0.083 mg mL^{-1} in MeOH, λ_{max} / nm, (ϵ / $\text{dm}^2 \text{mol}^{-1}$): 288 (4.54×10^4), 488 (1.27×10^4); E_{c1} : -1.201 V, E_{a1} : -1.133 V, E_{c2} : -1.859 V, E_{a2} : -1.713 V, E^0_1/Fc : -1.168 V; $[\alpha]_{\text{D}}^{20}$ (*c*: 0.083 mg mL^{-1} in MeOH): 0.

2-(Allylamino)-6-(((1*R*,2*S*,4*aS*,8*aS*)-1,2,4*a*,5-tetramethyl-1,2,3,4,4*a*,7,8,8*a*-octahydronaphthalen-1-yl)methyl)cyclohexa-2,5-diene-1,4-dione (**8a**). The compound was separated from its regioisomer by low-bar chromatography using petroleum ether (b.p. 40–60 °C):ethyl acetate (85:15) as eluent (R_{f} : 0.27) and purified by preparative thin-layer chromatography using petroleum ether:ethyl acetate (8:2) as eluent (R_{f} : 0.44) three times, due to close proximity with avarol as a side product (R_{f} : 0.36), leading to the low yield.

Yield 25.3 mg; 7.2 %; reddish brown oil; IR (ATR, cm^{-1}): 3390, 3298, 2960, 1670, 1633, 1585, 1501, 1441, 1380, 1344, 1289, 1247, 1189, 1093, 1028, 914, 801, 632, 442; $^1\text{H-NMR}$ (200 MHz, CDCl_3 , δ / ppm): 6.37 (1H, *d*, $J = 2$ Hz, C6'-H), 5.70–6.00 (2H, *m*, C2''-H & C4'-NH), 5.44 (1H, *d*, $J = 2$ Hz, C4'-H), 5.31 (1H, *m*, C3''-H_a), 5.23 (1H, *t*, $J = 2$ Hz, C3''-H_b), 5.14 (1H, *s*, C3-H), 3.74 (2H, *t*, $J = 6$ Hz, C1''-H₂), 2.63 (1H, *d*, $J = 14$ Hz, C15-H_a), 2.38 (1H, *d*, $J = 12$ Hz, C15-H_b), 1.80–2.10 (4H, *m*, C2-H₂ & C6-H₂), 1.10–1.70 (9H, *m*, C1-H₂, C7-H₂, C8-H, C10-H & C11-H₃), 0.80–1.10 (9H, *m*, C14-H₃, C13-H₃ & C12-H₃); $^{13}\text{C-NMR}$ (50 MHz, CDCl_3 , δ / ppm): 185.6 (C5'), 183.9 (C2'), 146.6 (C3'), 144.0 (C4), 142.2 (C1'), 139.6 (C6'), 131.7 (C2''), 120.6 (C3), 118.3 (C3''), 98.5 (C4'), 46.7 (C10), 45.0 (C1''), 42.0 (C5), 38.4 (C9), 36.6 (C8), 36.0 (C6), 35.0 (C15), 27.4 (C7), 26.5 (C2), 20.0 (C12), 19.3 (C1), 18.0 (C11), 17.6 (C14), 16.7 (C13); (+)ESI-HRMS (*m/z*) calcd. for $[\text{C}_{24}\text{H}_{33}\text{NO}_2+\text{H}^+]$: 368.25841. Found: 368.25854; calcd. for $[\text{C}_{24}\text{H}_{33}\text{NO}_2+\text{Na}^+]$: 390.24035. Found: 390.24116; UV–Vis (*c*: 0.083 mg mL^{-1} in MeOH, λ_{max} / nm, (ϵ / $\text{dm}^2 \text{mol}^{-1}$): 286 (2.19×10^4), 484 (0.97×10^4);

E_{c1} : -1.170 V, E_{a1} : -1.113 V, E_{c2} : -1.830 V, E_{a2} : -1.741 V, E_1° / Fc : -1.142 V; $[\alpha]_D^{20}$ (c : 0.083 mg mL⁻¹ in MeOH): -50.

2-(Allylamino)-5-(((1*R*,2*S*,4*aS*,8*aS*)-1,2,4*a*,5-tetramethyl-1,2,3,4,4*a*,7,8,8*a*-octahydronaphthalen-1-yl)methyl)cyclohexa-2,5-diene-1,4-dione (**8b**). The compound was separated from its regioisomer by low-bar chromatography using petroleum ether (b.p. 40–60 °C):ethyl acetate (9:1) as eluent (R_f : 0.35) and purified by preparative thin-layer chromatography using petroleum ether:ethyl acetate (8:2) as eluent (R_f : 0.61).

Yield: 58.5 mg; 16.6 %; reddish brown oil; IR (ATR, cm⁻¹): 3332, 3083, 2925, 1663, 1624, 1586, 1506, 1448, 1379, 1339, 1312, 1256, 1224, 1205, 1099, 1037, 916, 841, 799, 567, 460; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 6.37 (1H, *s*, C6'-H), 5.85 (1H, *m*, C2''-H), 5.61 (1H, *bs*, C4'-NH), 5.46 (1H, *s*, C3'-H), 5.30 (1H, *m*, C3''-H_a), 5.24 (1H, *t*, $J = 2$ Hz, C3''-H_b), 5.15 (1H, *s*, C3-H), 3.73 (2H, *t*, $J = 6$ Hz, C1''-H₂), 2.65 (1H, *d*, $J = 14$ Hz, C15-H_a), 2.47 (1H, *d*, $J = 14$ Hz, C15-H_b), 1.80–2.10 (4H, *m*, C2-H₂ & C6-H₂), 1.10–1.70 (9H, *m*, C1-H₂, C7-H₂, C8-H, C10-H & C11-H₃), 0.80–1.10 (9H, *m*, C14-H₃, C13-H₃ & C12-H₃); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 185.4 (C2'), 183.5 (C5'), 151.1 (C1'), 145.8 (C4'), 144.0 (C4), 131.8 (2C, C6' and C2''), 120.7 (C3), 118.2 (C3''), 99.1 (C3'), 47.2 (C10), 44.7 (C1''), 43.1 (C5), 38.5 (C9), 37.1 (C8), 36.1 (C6), 35.7 (C15), 27.5 (C7), 26.5 (C2), 20.0 (C12), 19.4 (C1), 18.0 (C11), 17.7 (C14), 16.8 (C13); (+)ESI-HRMS (m/z) calcd. for [C₂₄H₃₃NO₂+H⁺]: 368.25841. Found: 368.2534; calcd. for [C₂₄H₃₃NO₂+Na⁺]: 390.24035. Found: 390.24053; UV-Vis (c : 0.083 mg mL⁻¹ in MeOH, λ_{max} / nm, (ϵ / dm² mol⁻¹): 286 (4.14×10⁴), 480 (1.05×10⁴); E_{c1} : -1.177 V, E_{a1} : -1.117 V, E_{c2} : -1.799 V, E_{a2} : -1.689 V, E_1° / Fc : -1.150 V; $[\alpha]_D^{20}$ (c : 0.083 mg mL⁻¹ in MeOH): +70.

2-(Pyrrolidin-1-yl)-6-(((1*R*,2*S*,4*aS*,8*aS*)-1,2,4*a*,5-tetramethyl-1,2,3,4,4*a*,7,8,8*a*-octahydronaphthalen-1-yl)methyl)cyclohexa-2,5-diene-1,4-dione (**9a**). The compound was separated from its regioisomer by low-bar chromatography using petroleum ether (b.p. 40–60 °C):ethyl acetate (8:2) as eluent (R_f : 0.18) and purified by preparative thin-layer chromatography using petroleum ether:ethyl acetate (7:3) as eluent (R_f : 0.22).

Yield: 96.4 mg; 26.3 %; reddish brown crystals; m.p.: 121°C; IR (ATR, cm⁻¹): 3323, 2961, 1670, 1635, 1589, 1559, 1454, 1415, 1379, 1335, 1284, 1262, 1189, 1098, 1025, 912, 861, 800, 755; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 6.36 (1H, *d*, $J = 2$ Hz, C6'-H), 5.42 (1H, *d*, $J = 2$ Hz, C4'-H), 5.13 (1H, *s*, C3-H), 3.52 (4H, *m*, C1''-H₂ & C4''-H₂), 2.67 (1H, *d*, $J = 4$ Hz, C15-H_a), 2.37 (1H, *d*, $J = 6$ Hz, C15-H_b), 1.90–2.10 (8H, *m*, C2-H₂; C6-H₂; C2''-H₂ & C3''-H₂), 1.10–1.70 (9H, *m*, C1-H₂, C7-H₂, C8-H, C10-H & C11-H₃), 0.80–1.10 (9H, *m*, C14-H₃, C13-H₃ & C12-H₃); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 185.6 (C5'), 185.0 (C2'), 148.6 (C3'), 144.3 (C4), 143.1 (C1'), 138.5 (C6'), 120.8 (C3), 101.8 (C4'), 50.9 (2C, C1'' & C4''), 47.0 (C10), 42.2 (C5), 38.9 (C9), 36.9 (C8), 36.2

(C6), 35.3 (C15), 27.6 (C7), 26.8 (2C, C2" & C3"), 20.2 (C2), 19.4 (C12), 18.3 (C1), 17.9 (C11), 17.0 (C14), 16.9 (C13); (+)ESI-HRMS (m/z) calcd. for $[C_{25}H_{35}NO_2+H]^+$: 382.27406. Found: 382.27388; UV-Vis (c : 0.083 mg mL⁻¹ in MeOH, λ_{max} / nm, (ϵ / dm² mol⁻¹): 292 (2.79×10⁴), 506 (2.14×10⁴); E_{c1} : -1.267 V, E_{a1} : -1.163 V, E_{c2} : -1.883 V, E_{a2} : -1.710 V, E°_1 / Fc : -1.217 V; $[\alpha]_D^{20}$ (c : 0.083 mg mL⁻¹ in MeOH): +60.

2-(Pyrrolidin-1-yl)-5-(((1R,2S,4aS,8aS)-1,2,4a,5-tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl)methyl)cyclohexa-2,5-diene-1,4-dione (**9b**). The compound was separated from its regioisomer by low-bar chromatography using petroleum ether (b.p. 40–60 °C):ethyl acetate (9:1) as eluent (R_f : 0.32) and purified by preparative thin-layer chromatography using petroleum ether:ethyl acetate (8:2) as eluent (R_f : 0.45).

Yield: 48.6 mg; 13.2 %; reddish brown crystals; m.p.: 42 °C; IR (ATR, cm⁻¹): 3330, 2961, 1662, 1630, 1562, 1451, 1380, 1260, 1227, 1096, 1024, 801, 757; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 6.26 (1H, *s*, C6'-H), 5.44 (1H, *s*, C3'-H), 5.15 (1H, *s*, C3-H), 3.54 (4H, *m*, C1"-H₂ & C4"-H₂), 2.63 (1H, *d*, J = 6 Hz, C15-H_a), 2.46 (1H, *d*, J = 6 Hz, C15-H_b), 1.90–2.10 (8H, *m*, C2-H₂, C6-H₂, C2"-H₂ & C3"-H₂), 1.10–1.70 (9H, *m*, C1-H₂, C7-H₂, C8-H, C10-H & C11-H₃), 0.80–1.10 (9H, *m*, C14-H₃, C13-H₃ & C12-H₃); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 185.3 (C2'), 184.8 (C5'), 149.5 (C1'), 147.0 (C4'), 144.2 (C4), 133.2 (C6'), 121.0 (C3), 102.3 (C3'), 50.6 (2C, C1" & C4"), 47.4 (C10), 43.1 (C5), 38.7 (C9), 37.2 (C8), 36.4 (C6), 35.5 (C15), 27.8 (C7), 26.8 (2C, C2" & C3"), 20.2 (C2), 19.6 (C12), 18.3 (C1), 18.0 (C11), 17.0 (C14), 14.4 (C13); (+)ESI-HRMS (m/z) calcd. for $[C_{25}H_{35}NO_2+H]^+$: 382.27406. Found: 382.27420; UV-Vis (c : 0.083 mg mL⁻¹ in MeOH, λ_{max} / nm (ϵ / dm² mol⁻¹): 294 (2.79×10⁴), 506 (2.14×10⁴); E_{c1} : -1.259 V, E_{a1} : -1.177 V, E_{c2} : -1.861 V, E_{a2} : -1.704 V, E°_1 / Fc = -1.218 V. $[\alpha]_D^{20}$ (c : 0.083 mg mL⁻¹ in MeOH): +30.

2-(Benzylamino)-6-(((1R,2S,4aS,8aS)-1,2,4a,5-tetramethyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-yl)methyl)cyclohexa-2,5-diene-1,4-dione (**10a**). The compound was separated from its regioisomer by column chromatography using toluene as eluent (R_f : 0.19) and purified by preparative thin-layer chromatography using hexane:acetone (7:3) as eluent (R_f : 0.61).

Yield: 24.8 mg; 6.2 %; reddish brown crystals; m.p.: 85 °C; IR (ATR, cm⁻¹): 3388, 2960, 1670, 1635, 1587, 1503, 1455, 1380, 1346, 1251, 1189, 1095, 1072, 1028, 913, 803, 736, 699; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 7.20–7.50 (5H, *m*, C3"-H, C4"-H, C5"-H, C6"-H & C7"-H), 6.38 (1H, *d*, J = 2.4 Hz, C6'-H), 5.93 (1H, *bs*, C3'-NH), 5.49 (1H, *d*, J = 1.6 Hz, C4'-H), 5.14 (1H, *s*, C3-H), 4.27 (2H, *d*, J = 5.6 Hz, C1"-H₂), 2.63 (1H, *d*, J = 14 Hz, C15-H_b), 2.39 (1H, *d*, J = 14 Hz, C15-H_a), 1.80–2.20 (4H, *m*, C2-H₂ & C6-H₂), 1.20–1.80 (12H, *m*, C1-H₂, C7-H₂, C8-H, C10-H, C11-H₃ & C12-H₃), 0.80–1.10 (6H, *m*, C13-H₃ & C14-H₃); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 185.7 (C5'), 183.9 (C2'), 146.6

(C3'), 144.0 (C4), 142.2 (C1'), 139.6 (C6'), 135.9 (C2''), 129.0 (2C, C4'' & C6''), 128.1 (2C, C3'' & C7''), 127.7 (C5''), 120.6 (C3), 98.6 (C4'), 46.9 (C1''), 46.7 (C10), 42.1 (C5), 38.4 (C9), 36.6 (C8), 36.0 (C6), 35.0 (C15), 27.3 (C7), 26.5 (C2), 20.0 (C12), 19.3 (C1), 18.0 (C11), 17.7 (C14), 16.6 (C13); (+)ESI-HRMS (m/z) calcd. for $[C_{28}H_{35}NO_2+H^+]$: 418.27406. Found: 418.27452; UV-Vis (c : 0.083 mg mL⁻¹ in MeOH, λ_{max} / nm, (ϵ / dm² mol⁻¹): 288 (4.21×10^4), 488 (1.89×10^4). E_{c1} : -1.115 V, E_{a1} : -1.043 V, E_{c2} : -1.865 V, E_{a2} : -1.733 V, E_1° / Fc : -1.147V; $[\alpha]_D^{20}$ (c : 0.083 mg mL⁻¹ in MeOH): +10.

2-(Benzylamino)-5-(((1*R*,2*S*,4*aS*,8*aS*)-1,2,4*a*,5-tetramethyl-1,2,3,4,4*a*,7,8,8*a*-octahydronaphthalen-1-yl)methyl)cyclohexa-2,5-diene-1,4-dione (**10b**). The compound was separated from its regioisomer by column chromatography using toluene as eluent (R_f : 0.36) and purified by preparative thin-layer chromatography using hexane:acetone (7:3) as eluent (R_f : 0.65).

Yield: 24.7 mg, 6.2 %; reddish brown crystals; m.p.: 107 °C; IR (ATR, cm⁻¹): 3383, 2933, 1666, 1628, 1530, 1512, 1454, 1380, 1314, 1245, 1222, 1099, 1030, 901, 839, 736, 699; ¹H-NMR (200 MHz, CDCl₃, δ / ppm): 7.20–7.50 (5H, *m*, C3''-H, C4''-H, C5''-H, C6''-H & C7''-H), 6.38 (1H, *s*, C6'-H), 5.80 (1H, *bs*, C4'-NH), 5.50 (1H, *s*, C3'-H), 5.16 (1H, *s*, C3-H), 4.26 (1H, *d*, $J = 5.8$ Hz, C1''-H₂), 2.65 (1H, *d*, $J = 12.8$ Hz, C15-H_b), 2.47 (1H, *d*, $J = 12.8$ Hz, C15-H_a), 1.80–1.20 (4H, *m*, C2-H₂ & C6-H₂), 1.20–1.80 (12H, *m*, C1-H₂, C7-H₂, C8-H, C10-H, C11-H₃ & C12-H₃), 0.80–1.10 (6H, *m*, C13-H₃ & C14-H₃); ¹³C-NMR (50 MHz, CDCl₃, δ / ppm): 185.4 (C2'), 183.5 (C5'), 151.1 (C4'), 145.8 (C4), 144.0 (C1'), 136.0 (C2''), 131.9 (C6'), 129.0 (2C, C4'' and C6''), 128.1 (2C, C3'' and C7''), 127.8 (C5''), 120.7 (C3), 99.2 (C3'), 47.1 (C10), 46.6 (C1''), 43.1 (C5), 38.5 (C9), 37.0 (C8), 36.0 (C6), 35.7 (C15), 27.5 (C7), 26.4 (C2), 20.0 (C12), 19.3 (C1), 18.0 (C11), 17.7 (C14), 16.8 (C13); (+)ESI-HRMS (m/z) calcd. for $[C_{28}H_{35}NO_2+H^+]$: 418.27406. Found: 418.27438; UV-Vis (c : 0.083 mg mL⁻¹ in MeOH, λ_{max} / nm, (ϵ / dm² mol⁻¹): 290 (7.57×10^4), 484 (2.02×10^4); E_{c1} : -1.123 V, E_{a1} : -1.054 V, E_{c2} : -1.840 V, E_{a2} : -1.685 V, E_1° / Fc : -1.157 V; $[\alpha]_D^{20}$ (c : 0.083 mg mL⁻¹ in MeOH): +50.