

Removal of hERG K⁺ channel affinity through rigidity – a case of Clofilium analogues

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Supplementary information

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3-(4-Chlorophenyl)prop-2-yn-1-ol 4: To a solution of 4-chloriodobenzene (5.96 g, 25 mmol) in THF (33 mL) and Et₃N (7.3 mL) were added PdCl₂(PPh₃)₂ (35 mg, 0.5 mmol) and Cul (327 mg, 1.7 mmol). The mixture was stirred for 30 minutes and a solution of propargyl alcohol (1.48 mL, 25 mmol) in THF (10 mL) was added dropwise. The mixture was stirred at r.t. for 12 hours and filtered on Celite. The solvents were evaporated and the crude residue was purified by flash chromatography on silica gel (10% EtOAc – Petroleum ether) to afford pure **4** (3.2 g, 77%) as an oil. Spectral data were in agreement with literature.¹

3-(4-Chlorophenyl)prop-2-yn-1-yl 4-methylbenzenesulfonate 5: To a stirred solution of **4** (830 mg, 5 mmol) in ether (32 mL) at 0 °C was added tosyl chloride (1.15 g, 6 mmol) followed, portionwise, by freshly powdered KOH (2.8 g, 50 mmol). After the addition was complete, the reaction mixture was stirred at room temperature for 3.5 h and then poured into water (65 mL). The layers were separated and the aqueous phase was extracted with EtOAc (3 × 30 mL). The combined organic extract was dried, filtered, concentrated *in vacuo* and chromatographed (25% EtOAc – Petroleum ether) to obtain the title compound **5** (1.54 g, 96%). ¹H NMR (400 MHz, CDCl₃) δ 7.85 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.19 (d, *J* = 8.6 Hz, 2H), 4.93 (s, 2H), 2.41 (s, 3H) ppm.

N-(3-(4-Chlorophenyl)prop-2-yn-1-yl)-N-ethylheptan-1-amine 6: To a solution of **5** (321 mg, 1 mmol) in DMF (5 mL) was added K₂CO₃ (415 mg, 3 mmol) followed by *N*-ethylheptylamine (190 μL, 1 mmol). The mixture was stirred at r.t. for 1 hour and diluted with water (5 mL), extracted with EtOAc (3 × 10 mL) and the organic layers were dried on MgSO₄, filtered and the solvent was removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel to afford pure **6** as an oil (218 mg, 75%). ¹H NMR (400 MHz, CDCl₃) δ 7.34 (d, *J* = 8.4 Hz, 2H), 7.26 (d, *J* = 8.4 Hz, 2H), 3.61 (s, 2H), 2.60 (q, *J* = 7.2 Hz, 2H), 2.52 (t, *J* = 7.6 Hz, 2H), 1.52–1.48 (m, 2H), 1.31–1.27 (m, 8H), 1.10 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 133.9, 132.9, 128.5, 121.9, 85.8, 83.9, 53.6, 47.7, 42.1, 31.8, 29.3, 27.6, 27.5, 22.7, 14.1, 12.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₈H₂₈Cl₂N : 292.1827, found : 292.1825; HPLC : *t*_R = 7.53 min.

N-(3-(4-Chlorophenyl)prop-2-yn-1-yl)-N,N-diethylheptan-1-aminium 4-methylbenzenesulfonate 7: To a solution of **5** (96 mg, 0.3 mmol) in CH₃CN (5 mL) was added *N,N*-diethylheptylamine (56 mg, 0.3 mmol). The mixture was stirred at r.t. for 24 hours and diluted with extracted with EtOAc (10 mL). The precipitated solid was filtered and dried *in*

¹ Y. Xie, M. Yu, Y. Zhang *Synthesis* **2011**, 2803-2809.

vacuo to afford pure **7** as a solid (50 mg, 38%). ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.4 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.0 Hz, 2H), 4.61 (s, 2H), 3.54 (q, *J* = 7.2 Hz, 4H), 3.32 (t, *J* = 8.4 Hz, 2H), 2.30 (s, 3H), 1.71 (br s, 2H), 1.40–1.24 (m, 14H), 0.85 (t, *J* = 6.6 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 141.8, 139.1, 136.3, 133.5, 129.1, 128.6, 126.1, 119.0, 90.2, 77.4, 58.5, 54.5, 49.9, 31.7, 28.8, 26.5, 22.6, 22.3, 21.4, 14.1, 8.3 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₂₀H₃₁ClN : 320.2140, found : 320.2137; HPLC : *t*_R = 7.57 min.

General procedure for the synthesis of derivatives 12-15 :² To a solution of ethynyltrimethylsilane (5.6 mL, 40 mmol) in THF (20 mL) at 0 °C as added *i*-PrMgCl (2 M solution in THF, 20 mL, 40 mmol) dropwise. The mixture was then stirred for 30 minutes at 0 °C and 30 minutes at r.t.. CuBr (860 mg, 6 mmol) was then added in one portion and the mixture was stirred at r.t. for an additional 30 minutes, upon which benzyl bromide **8-11** (10 mmol) was added. The mixture was then refluxed for 4.5 hours and poured onto a saturated aqueous NH₄Cl solution (400 mL). The mixture was extracted with Et₂O (2 x 500 mL), the organic layers were gathered and washed with water (400 mL), dried on MgSO₄, filtered and the solvents were removed *in vacuo*. The crude residue was purified by flash chromatography on silica gel (0.5% EtOAc – Petroleum ether) to compounds **12-15** as oils.

Trimethyl(3-phenylprop-1-yn-1-yl)silane 12 : 1.47 g (80%). Spectral data were in agreement with literature.²

(3-(4-Chlorophenyl)prop-1-yn-1-yl)trimethylsilane 13 : 1.97 g (89%). Spectral data were in agreement with literature.³

Trimethyl(3-(*p*-tolyl)prop-1-yn-1-yl)silane 14 : 1.8 g (91%). ¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 3.61 (s, 2H), 2.33 (s, 3H), 0.18 (s, 9H) ppm.

(3,3-Diphenylprop-1-yn-1-yl)trimethylsilane 15 : 2.16 g (82%). Spectral data were in agreement with literature.⁴

General procedure for the synthesis of derivatives 16-19 :⁵ To a solution of **12-15** (8 mmol) in MeOH (40 mL) at 0 °C was added K₂CO₃ (5.5 g, 40 mmol). The mixture was stirred at 0 °C for 2 h and water (20 mL) was added. The solution was allowed to warm to room temperature, the layers were separated and the aqueous one was extracted with Et₂O (3 x 60 mL). The organic phases were gathered and washed with water (2 x 15 mL), brine (15 mL), dried over MgSO₄, and the solvents were removed *in vacuo*. The obtained products **16-19** were used in the next step without further purification.

General procedure for the synthesis of compounds 20-26, 34-39, 46-47 and 52-55 : To a solution of alkyne (**16-19**, **31-33**, **45**, **50-51**) (1 mmol) in 1,4-dioxane (1 mL) were added paraformaldehyde (32 mg, 1.05 mmol), copper (II) acetate hydrate (21 mg, 0.105 mmol) and amine (1.05 mmol). The mixture was stirred at 90 °C for 12 hours, filtered, and the filtrate was purified by flash chromatography on silica gel (5% to 50% EtOAc – Petroleum ether) to afford **20-26**, **34-39**, **46-47** and **52-55** as oils.

***N*-Butyl-*N*-ethyl-4-phenylbut-2-yn-1-amine 20** : 314 mg (69%). ¹H NMR (400 MHz, CDCl₃) δ 7.34–7.26 (m, 4H), 7.23–7.18 (m, 1H), 3.61 (t, *J* = 2 Hz, 2H), 3.43 (t, *J* = 2 Hz, 2H), 2.54 (q, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 7.6 Hz, 2H), 1.48–1.40 (m, 2H), 1.36–1.27 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 137.2, 128.5, 127.9,

² T. Hameury, J. Guillemont, L. V. Hijfte, V. Bellosta, J. Cossy *Org. Lett.* **2009**, *11*, 2397-2400.

³ C. H. Larsen, K. W. Anderson, R. E. Tundel, S. L. Buchwald *Synlett* **2006**, 2941-2946.

⁴ N. A. Porter, D. J. Hogenkamp, F. F. Khouri *J. Am. Chem. Soc.* **1990**, *112*, 2402 – 2407.

⁵ C. Séguin, F. Ferreira, C. Botuha, F. Chemla, A. Pérez-Luna *J. Org. Chem.* **2009**, *74*, 6986-6992.

126.5, 82.3, 77.1, 53.3, 47.7, 41.7, 35.5, 29.7, 20.8, 14.1, 12.7 ppm; HRMS (ESI) : m/z [$M + H$]⁺ calcd for C₁₆H₂₄N : 230.1903, found : 230.1901.

N-Ethyl-N-heptyl-4-phenylbut-2-yn-1-amine 21 : 1.2 g (89%). ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.29 (m, 4H), 7.22 (t, $J = 6.8$ Hz, 1H), 3.63 (s, 2H), 3.45 (t, $J = 1.6$ Hz, 2H), 2.56 (q, $J = 14.4$, 7.2 Hz, 2H), 2.47 (t, $J = 8.8$ Hz, 2H), 1.49–1.45 (m, 2H), 1.29–1.24 (m, 8H), 1.07 (t, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 6.8$ Hz) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 137.3, 128.5, 127.9, 126.6, 82.3, 53.7, 47.4, 41.7, 32.0, 29.4, 27.7, 27.6, 25.2, 22.8, 14.2, 12.8 ppm; HRMS (ESI) : m/z [$M + H$]⁺ calcd for C₁₉H₃₀N : 272.2372, found: 272.2373; HPLC $t_R = 14.2$ min.

N-Butyl-4-(4-chlorophenyl)-N-ethylbut-2-yn-1-amine 22 : 288 mg (55%). ¹H NMR (400 MHz, CDCl₃) δ 7.27 (s, 4H), 3.58 (t, $J = 2.0$ Hz, 2H), 3.44 (t, $J = 2.0$ Hz, 2H), 2.54 (q, $J = 7.2$ Hz, 2H), 2.48–2.44 (m, 2H), 1.48–1.41 (m, 2H), 1.36–1.27 (m, 2H), 1.06 (t, $J = 7.2$ Hz, 3H), 0.91 (t, $J = 7.2$ Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 135.8, 132.4, 129.3, 128.6, 81.8, 77.6, 53.3, 47.7, 41.8, 29.8, 24.7, 20.9, 14.2, 12.7 ppm; HRMS (ESI) : m/z [$M + H$]⁺ calcd for C₁₆H₂₃ClN : 264.1514, found: 264.1515; HPLC $t_R = 14.2$ min.

N-Ethyl-4-(4-chlorophenyl)-N-heptylbut-2-yn-1-amine 23 : 337 mg (55%). ¹H NMR (400 MHz, CDCl₃) δ 7.26 (s, 4H), 3.57 (s, 2H), 3.42 (t, $J = 2.0$ Hz, 2H), 2.53 (q, $J = 7.2$ Hz, 2H), 2.44 (t, $J = 7.6$ Hz, 2H), 1.46–1.43 (m, 2H), 1.35–1.20 (m, 8H), 1.05 (t, $J = 7.2$ Hz, 3H), 0.86 (t, $J = 7.2$ Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 135.8, 132.4, 129.3, 128.6, 81.8, 77.6, 53.7, 47.7, 41.8, 32.0, 29.4, 27.7, 27.6, 24.7, 22.8, 14.2, 12.8 ppm; HRMS (ESI) : m/z [$M + H$]⁺ calcd for C₁₉H₂₉ClN : 306.1983, found: 306.1984; HPLC $t_R = 14.8$ min.

N-Butyl-N-ethyl-4-(p-tolyl)but-2-yn-1-amine 24 : 173 mg (71%). ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 3.58 (t, $J = 2$ Hz, 2H), 3.44 (t, $J = 2$ Hz, 2H), 2.55 (q, $J = 7.2$ Hz, 2H), 2.48 (t, $J = 7.6$ Hz, 2H), 2.32 (s, 3H), 1.49–1.40 (m, 2H), 1.37–1.28 (m, 2H), 1.06 (t, $J = 7.2$ Hz, 3H), 0.92 (t, $J = 7.2$ Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 136.1, 134.3, 129.2, 127.8, 82.6, 76.9, 53.3, 47.7, 41.8, 29.8, 24.8, 21.1, 20.9, 14.2, 12.8 ppm; HRMS (ESI) : m/z [$M + H$]⁺ calcd for C₁₇H₂₆N : 244.2060, found: 244.2058; HPLC $t_R = 13.3$ min.

N-Ethyl-N-heptyl-4-(p-tolyl)but-2-yn-1-amine 25 : 188 mg (66%). ¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, $J = 8.0$ Hz, 2H), 7.11 (d, $J = 8.0$ Hz, 2H), 3.57 (t, $J = 2$ Hz, 2H), 3.43 (t, $J = 2$ Hz, 2H), 2.54 (q, $J = 7.2$ Hz, 2H), 2.46 (t, $J = 7.6$ Hz, 2H), 2.32 (s, 3H), 1.47–1.44 (m, 2H), 1.28 (br s, 8H), 1.06 (t, $J = 7.2$ Hz, 3H), 0.87 (t, $J = 7.2$ Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 136.1, 134.2, 129.2, 127.8, 82.6, 76.9, 53.6, 47.7, 41.8, 40.0, 29.4, 27.7, 27.6, 24.8, 22.7, 21.1, 14.2, 12.8 ppm; HRMS (ESI) : m/z [$M + H$]⁺ calcd for C₂₀H₃₂N : 286.2529, found: 286.2528.

N-(4,4-Diphenylbut-2-yn-1-yl)-N-ethylheptan-1-amine 26 : 132 mg (38%). ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.35 (m, 4H), 7.30–7.26 (m, 4H), 7.22–7.18 (m, 2H), 5.01 (s, 1H), 3.52 (d, $J = 2.0$ Hz, 2H), 2.56 (q, $J = 7.2$ Hz, 2H), 2.51–2.47 (m, 2H), 1.51–1.45 (m, 2H), 1.28–1.26 (m, 8H), 1.07 (t, $J = 7.2$ Hz, 3H), 0.88 (t, $J = 7.2$ Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 142.3, 128.6, 127.9, 126.9, 85.6, 79.6, 53.7, 47.9, 43.5, 41.8, 32.0, 29.5, 27.7, 27.6, 22.8, 14.3, 12.8 ppm; HRMS (ESI) : m/z [$M + H$]⁺ calcd for C₂₅H₃₄N : 348.2686, found: 348.2686; HPLC $t_R = 13.3$ min.

N-Butyl-N-ethyl-5-phenylpent-2-yn-1-amine 34 : 895 mg (74%). ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.24 (m, 2H), 7.21–7.18 (m, 3H), 3.33 (t, $J = 2$ Hz, 2H), 2.80 (t, $J = 7.6$ Hz, 2H), 2.50–2.42 (m, 4H), 2.37 (t, $J = 7.6$ Hz, 2H), 1.43–1.36 (m, 2H), 1.33–1.28 (m, 2H), 1.01 (t, $J = 7.2$ Hz, 3H), 0.90 (t, $J = 7.2$ Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 140.9, 128.6, 128.4, 126.3, 84.2, 75.5, 53.2, 47.5, 41.7, 35.5, 29.8, 21.0, 20.9, 14.2, 12.7 ppm; HRMS (ESI) : m/z [$M + H$]⁺ calcd for C₁₇H₂₆N : 244.2060, found: 244.2058; HPLC $t_R = 12.9$ min.

N-Ethyl-N-(5-phenylpent-2-yn-1-yl)heptan-1-amine 35 : 82 mg (29%). ¹H NMR (400 MHz, CDCl₃) δ 7.28 (dd, *J* = 7.2, 1.2 Hz, 2H), 7.23–7.18 (m, 3H), 3.35 (t, *J* = 2.0 Hz, 2H), 2.81 (t, *J* = 4.4 Hz, 2H), 2.52–2.44 (m, 4H), 2.38 (q, *J* = 9.2, 7.2 Hz, 2H), 1.44–1.40 (m, 2H), 1.33–1.24 (m, 8H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 140.9, 128.5, 128.4, 126.3, 108.5, 84.2, 75.3, 53.5, 47.4, 41.6, 35.4, 31.9, 31.0, 29.4, 27.7, 27.5, 22.7, 20.9, 14.2, 12.6 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₂₀H₃₂N : 286.2528, found: 286.2529; HPLC *t*_R = 15.0 min.

N-Butyl-5-(4-chlorophenyl)-N-ethylpent-2-yn-1-amine 36 : 247 mg (45%). ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 4.2 Hz, 2H), 7.14 (d, *J* = 4.2 Hz, 2H), 3.33 (t, *J* = 2.0 Hz, 2H), 2.77 (t, *J* = 7.2 Hz, 2H), 2.49–2.42 (m, 4H), 2.38–2.35 (m, 2H), 1.42–1.36 (m, 2H), 1.34–1.25 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 139.3, 132.1, 130.0, 128.5, 83.8, 75.8, 53.2, 47.5, 41.6, 34.7, 29.7, 20.9, 20.8, 14.2, 12.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₇H₂₅ClN : 268.1670, found: 268.1671; HPLC *t*_R = 13.6 min.

N-(5-(4-Chlorophenyl)pent-2-yn-1-yl)-N-ethylheptan-1-amine 37 : 263 mg (48%). ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, *J* = 4.2 Hz, 2H), 7.15 (d, *J* = 4.2 Hz, 2H), 3.34 (t, *J* = 2.0 Hz, 2H), 2.78 (t, *J* = 7.2 Hz, 2H), 2.50–2.42 (m, 4H), 2.38–2.34 (m, 2H), 1.45–1.38 (m, 2H), 1.37–1.20 (m, 8H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 139.3, 132.1, 130.0, 128.5, 83.7, 75.9, 53.5, 47.5, 41.6, 34.7, 32.0, 29.4, 27.7, 27.6, 22.8, 20.8, 14.2, 12.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₂₀H₃₁ClN : 320.2140, found: 320.2141; HPLC *t*_R = 13.8 min.

N-Butyl-N-ethyl-5-(*p*-tolyl)pent-2-yn-1-amine 38 : 193 mg (29%). ¹H NMR (400 MHz, CDCl₃) δ 7.11–7.06 (m, 4H), 3.34 (t, *J* = 2 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.49–2.44 (m, 4H), 2.39 (t, *J* = 7.6 Hz, 2H), 2.30 (s, 3H), 1.44–1.37 (m, 2H), 1.34–1.25 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 137.9, 135.7, 129.1, 128.4, 84.3, 75.4, 53.2, 47.5, 41.7, 35.1, 29.8, 21.1 (2 peaks), 21.0, 20.9, 14.2, 12.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₈H₂₈N : 258.2216, found: 258.2215; HPLC *t*_R = 13.6 min.

N-Ethyl-N-(5-(*p*-tolyl)pent-2-yn-1-yl)heptan-1-amine 39 : 281 mg (47%). ¹H NMR (400 MHz, CDCl₃) δ 7.11–7.07 (m, 4H), 3.34 (t, *J* = 2 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.49–2.44 (m, 4H), 2.38 (t, *J* = 7.6 Hz, 2H), 2.31 (s, 3H), 1.45–1.38 (m, 2H), 1.26 (m, 8H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 137.8, 135.7, 129.0, 128.4, 84.3, 75.3, 53.5, 47.4, 41.6, 35.0, 31.9, 29.3, 27.6 (2 peaks), 22.7, 21.0, 14.2 (2 peaks), 12.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₂₁H₃₄N : 300.2689, found: 300.2684; HPLC *t*_R = 14.9 min.

N-Butyl-4-(4-chlorophenoxy)-N-ethylbut-2-yn-1-amine 46 : 338 mg (60%). ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 4.8 Hz, 2H), 6.91 (d, *J* = 4.4 Hz, 2H), 4.70 (t, *J* = 2.0 Hz, 2H), 3.43 (t, *J* = 1.6 Hz, 2H), 2.48 (q, *J* = 14.4, 7.2 Hz, 2H), 2.39 (t, *J* = 8.0 Hz, 2H), 1.43–1.36 (m, 2H), 1.32–1.23 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.89 (t, *J* = 7.6 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 156.3, 129.4, 126.4, 116.5, 83.2, 79.3, 56.5, 53.3, 47.7, 41.5, 29.6, 20.8, 14.2, 12.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₆H₂₃ClNO : 280.1463, found: 280.1463; HPLC *t*_R = 13.3 min.

N-(4-(4-Chlorophenoxy)but-2-yn-1-yl)-N-ethylheptan-1-amine 47 : 480 mg (75%). ¹H NMR (400 MHz, CDCl₃) δ 7.24 (d, *J* = 4.4 Hz, 2H), 6.91 (d, *J* = 4.4 Hz, 2H), 4.70 (t, *J* = 1.6 Hz, 2H), 3.44 (t, *J* = 2.0 Hz, 2H), 2.49 (q, *J* = 14.4, 7.2 Hz, 2H), 2.39 (t, *J* = 8.8 Hz, 2H), 1.45–1.37 (m, 2H), 1.31–1.22 (m, 8H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 156.5, 129.4, 126.4, 117.1, 116.5, 83.1, 79.4, 56.6, 53.7, 47.7, 41.5, 32.0, 29.4, 27.6, 27.4, 22.8, 14.3, 12.6 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₉H₂₉ClNO : 322.1933, found: 322.1932; HPLC *t*_R = 14.5 min.

N-Butyl-4-((4-chlorobenzyl)oxy)-N-ethylbut-2-yn-1-amine 52 : 485 mg (78%). ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.26 (m, 4H), 4.56 (s, 2H), 4.20 (t, *J* = 2.0 Hz, 2H), 3.48 (t, *J* = 2.0 Hz, 2H), 2.56 (q, *J* = 7.2 Hz, 2H), 2.50–2.46 (m, 2H), 1.49–1.42 (m, 2H), 1.37–1.28 (m, 2H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 136.2, 133.7, 129.5, 128.7, 81.8, 80.5, 70.7, 57.7, 53.3, 47.7, 41.6, 29.7, 20.8, 14.2, 12.7 ppm; HRMS (ESI) : *m/z* [*M* + H]⁺ calcd for C₁₇H₂₅ClNO : 294.1619, found: 294.1619; HPLC *t*_R = 13.3 min.

N-(4-((4-Chlorobenzyl)oxy)but-2-yn-1-yl)-N-ethylheptan-1-amine 53 : ¹H NMR (400 MHz, CDCl₃) δ 7.33–7.27 (m, 4H), 4.56 (s, 2H), 4.20 (t, *J* = 2.0 Hz, 2H), 3.47 (t, *J* = 2.0 Hz, 2H), 2.54 (q, *J* = 7.2 Hz, 2H), 2.48–2.44 (m, 2H), 1.49–1.42 (m, 2H), 1.33–1.22 (m, 8H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 136.2, 133.7, 129.4, 128.7, 82.0, 80.3, 70.6, 57.7, 53.7, 47.7, 41.6, 32.0, 29.4, 27.7, 27.6, 22.8, 14.2, 12.8 ppm; HRMS (ESI) : *m/z* [*M* + H]⁺ calcd for C₂₀H₃₁ClNO : 336.2089, found: 336.2089; HPLC *t*_R = 14.6 min.

4-(Benzhydryloxy)-N-butyl-N-ethylbut-2-yn-1-amine 54 : 489 mg (74%). ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.28 (m, 8H), 7.25–7.22 (m, 2H), 5.68 (s, 1H), 4.17 (s, 2H), 3.46 (s, 2H), 2.53 (q, *J* = 7.2 Hz, 2H), 2.46 (t, *J* = 7.6 Hz, 4H), 1.48–1.40 (m, 2H), 1.36–1.24 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 141.5, 128.5, 127.7, 127.4, 81.7, 81.4, 80.6, 56.3, 53.4, 47.7, 41.6, 29.8, 20.8, 14.2, 12.8 ppm; HRMS (ESI) : *m/z* [*M* + H]⁺ calcd for C₂₃H₃₀NO : 336.2322, found: 336.2321; HPLC *t*_R = 13.5 min.

N-(4-(Benzhydryloxy)but-2-yn-1-yl)-N-ethylheptan-1-amine 55 : 526 mg (70%). ¹H NMR (400 MHz, CDCl₃) δ 7.39–7.30 (m, 5H), 7.27–7.23 (m, 5H), 5.70 (s, 1H), 4.19 (t, *J* = 1.6 Hz, 2H), 3.47 (t, *J* = 1.6 Hz, 2H), 2.55 (q, 7.2 Hz, 2H), 2.47 (t, *J* = 7.2 Hz, 2H), 1.50–1.45 (m, 2H), 1.29–1.23 (m, 8H), 1.07 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 141.5, 128.5, 127.7, 127.4, 81.6, 81.4, 80.7, 56.3, , 53.7, 47.7, 41.6, 32.0, 29.4, 27.7, 22.7, 21.1, 14.3, 12.8 ppm; HRMS (ESI) : *m/z* [*M* + H]⁺ calcd for C₂₆H₃₇NO : 387.2795, found: 378. 2791; HPLC *t*_R = 15.2 min.

General procedure for the esterification of carboxylic acids 27, 28, 86 and 87 : A mixture of carboxylic acid (20 mmol), dimethyl carbonate (36 mmol) and conc. H₂SO₄ (96%) (100 μL, 0.2 mmol) was heated under magnetic stirring at 85 °C for 12 h. The reaction mixture was poured into 10% aq. NaHCO₃ (800 mg in 8 mL water) under stirring. The product was extracted into EtOAc, and the extract was washed with brine, dried (Na₂SO₄) and stripped of solvent *in vacuo*. The residue was purified by flash chromatography on silica gel (20% EtOAc – Petroleum ether) to afford pure esters **29**, **30**, **88** and **89**.

Methyl 3-(4-chlorophenyl)propanoate 29 : 5.3 g (95%). Spectral data was in agreement with literature.⁶

Methyl 3-(*p*-tolyl)propanoate 30 : 2.7 g (81%). Spectral data was in agreement with literature.⁷

Methyl 4-(4-chlorophenyl)butanoate 88 : 7.1 g (96%). Spectral data was in agreement with literature.⁸

Methyl 5-(4-chlorophenyl)pentanoate 89 : 2.3 g (100%). ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 3.66 (s, 3H), 2.59 (t, *J* = 7.2 Hz, 2H), 2.33 (t, *J* = 6.8 Hz, 2H), 1.64–1.61 (m, 4H) ppm.

⁶ T. O. Vieira, M. J. Green, H. Alper *Org. Lett.* **2006**, 8, 6143-6145.

⁷ I. Shibata, T. Suwa, K. Ryu, A. Bada *J. Org. Chem.* **2001**, 66, 8690-8692.

⁸ R. A. Bunce, A. N. Cox *Org. Prep. Proced. Int.* **2010**, 42, 83-93.

General procedure for the conversion of esters 29, 30 into alkynes 32, 33 : To a solution of ester (16.2 mmol) in CH₂Cl₂ (30 mL) at -78 °C was added DIBAL-H (1.2 M in toluene, 15.2 mL, 18.2 mmol) dropwise. The reaction mixture was stirred at -78 °C for 2 hours and MeOH (15 mL) was added. The reaction was warmed to 0 °C and K₂CO₃ (4.2 g, 30.4 mmol) followed by Ohira-Bestmann's reagent (3.8 g, 18.2 mmol) and MeOH (15 mL) were added. The mixture was stirred at r.t. for 12 hours and sat. aqueous. Rochelle salts (60 mL) and Et₂O (120 mL) were added. After 1 hour of stirring, the layers were separated, the organic one was washed with brine (30 mL), dried over MgSO₄ and the solvents were removed *in vacuo*. The obtained oil (**32** or **33**) was used in the next step without further purification.

N-Ethyl-N-(prop-2-yn-1-yl)butan-1-amine 41 : To a solution of amine **40** (6.8 mL, 50 mmol) in acetone (100 mL) were added K₂CO₃ (6.9 g, 50 mmol) followed by propargyl bromide (80% w/w in toluene, 5 mL, 45.5 mmol). The mixture was heated under reflux for 15 hours, the solids were filtered and the solvents removed *in vacuo* to afford **41** (4.5 g, 72%) as an oil that was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃) δ 3.42 (d, *J* = 2.4 Hz, 2H), 2.54 (q, *J* = 7.2 Hz, 2H), 2.47 (t, *J* = 7.4 Hz, 2H), 2.16 (t, *J* = 2.4 Hz, 1H), 1.48–1.41 (m, 2H), 1.38–1.28 (m, 2H), 1.06 (t, *J* = 7.2 Hz, 3H), 0.92 (t, *J* = 7.4 Hz, 3H) ppm.

General procedure for the oxidative coupling of phenylacetylenes and propargylamines : Alkyne **41** (446 mg, 3.2 mmol), 4-substituted phenylacetylene (0.64 mmol) and Cu(OAc)₂·H₂O (13 mg, 0.064 mmol) were dissolved in CH₂Cl₂ (5 mL). Piperidine (0.2 mL, 1.9 mmol) was added and a balloon with air was put on the flask. After 48 hours at 25 °C, the mixture was concentrated *in vacuo* and purified by Preparative TLC (20% EtOAc – Petroleum ether) yielding diyne **42, 43**.

N-Butyl-5-(4-chlorophenyl)-N-ethylpenta-2,4-diyn-1-amine 42 : 25 mg (14%). ¹H NMR (400 MHz, CDCl₃) δ 7.42 (d, *J* = 8.8 Hz, 2H), 7.29 (d, *J* = 8.8 Hz, 2H), 3.59 (s, 2H), 2.58 (q, *J* = 7.2 Hz, 2H), 2.51 (t, *J* = 7.2 Hz, 2H), 1.48–1.44 (m, 2H), 1.37–1.32 (m, 2H), 1.09 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 135.3, 133.9, 128.9, 120.4, 80.1, 75.0, 74.8, 69.4, 53.5, 47.9, 42.2, 29.9, 20.8, 14.2, 12.9 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₇H₂₁ClN : 274.1359, found : 274.1357; HPLC *t*_R = 14.0 min.

N-Butyl-N-ethyl-5-(p-tolyl)penta-2,4-diyn-1-amine 43 : 63 mg (25%). ¹H NMR (400 MHz, CDCl₃) δ 7.38 (d, *J* = 8.0 Hz, 2H), 7.12 (d, *J* = 8.0 Hz, 2H), 3.59 (s, 2H), 2.59 (q, *J* = 7.2 Hz, 2H), 2.53–2.49 (m, 2H), 2.35 (s, 3H), 1.48–1.43 (m, 2H), 1.37–1.33 (m, 2H), 1.08 (t, *J* = 7.2 Hz, 3H), 0.93 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 139.4, 132.5, 129.2, 118.6, 78.8, 76.1, 73.3, 69.7, 53.3, 47.7, 42.0, 29.7, 21.6, 20.7, 14.1, 12.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₇H₂₄N : 254.1903, found : 254.1902; HPLC *t*_R = 13.8 min.

1-Chloro-4-(prop-2-yn-1-yloxy)benzene 45 : To a solution of 4-chlorophenol **44** (5.25 mL, 53 mmol) and K₂CO₃ (29.4 g, 213 mmol) in acetone (150 mL) was added propargyl bromide (80% w/w in toluene, 4 mL, 56 mmol). The mixture was heated to reflux for 15 hours, filtered, and the volatiles were removed *in vacuo* to afford **45** (8.8 g, 99%) as an oil. Spectral data was in agreement with literature.⁹

General procedure for the propargylation of alcohols 48 and 49 : To a solution of alcohol (20 mmol) in DMF (100 mL) at 0 °C was added propargyl bromide (80% w/w in toluene, 4 mL, 25 mmol) followed by NaH (60% w/w in mineral oil, 1.08 g, 27 mmol). The mixture was stirred at r.t. for 2 hours and MeOH (10 mL) was added at 0 °C. The solvents were removed *in vacuo* and the residue was purified by flash chromatography on silica gel (20% EtOAc – Petroleum ether) to afford pure ethers **50** and **51**.

⁹ Y. Tsuzuki, T. K. N. Nguyen, B. Kuberan, D. R. Garud, M. Koketsu *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7269-7273.

1-Chloro-4-((prop-2-yn-1-yloxy)methyl)benzene 50 : 3.4 g (95%). Spectral data was in agreement with literature.¹⁰

((Prop-2-yn-1-yloxy)methylene)dibenzene 51 : 4.4 g (99%). ¹H NMR (400 MHz, CDCl₃) δ 7.37–7.31 (m, 8H), 7.28–7.25 (m, 2H), 5.57 (s, 1H), 4.16 (d, *J* = 2.4 Hz, 2H), 2.45 (t, *J* = 2.4 Hz, 1H) ppm.

(E)-Methyl 3-(4-chlorophenyl)acrylate 57 : To a solution of LiCl (1.45 g, 34 mmol) in CH₃CN (150 mL) was added trimethylphosphonoacetate (5.5 mL, 34 mmol) followed by DBU (5.25 mL, 35 mmol) and 4-chlorobenzaldehyde (4.03 g, 29 mmol). After one hour of stirring, Et₂O (300 mL) was added, and the organic layer was washed with 10% aq. HCl (100 mL), sat. aq. NaHCO₃ (100 mL), brine (100 mL), dried over MgSO₄, and the solvents were removed *in vacuo* to afford **57** as a white solid (4.51 g, 80%) that was used in the next step without further purification. Spectral data was in agreement with literature.¹¹

(E)-3-(4-Chlorophenyl)prop-2-en-1-ol 58 : To a solution of ester **57** (4.5 g, 23 mmol) in CH₂Cl₂ (60 mL) at –78 °C was added DIBAL-H (1M solution in CH₂Cl₂, 69 mL, 69 mmol) dropwise over 20 minutes. The reaction mixture was warmed to –40 °C and stirred for another 2 hours, upon which it was diluted with Et₂O (60 mL) and transferred to an erlenmyer flask containing Rochelle salts (1M, 25 g in 90 mL water). After 16 hours of vigorous stirring, the solution was extracted with Et₂O (3 x 45 mL). The organic layers were combined and washed with 10% aqueous HCl (90 mL), sat. aq. NaHCO₃ (45 mL), brine (45 mL) and dried over MgSO₄. The solvents were removed *in vacuo* and **58** (3.3 g, 85%) was obtained pure without further purification. Spectral data was in agreement with literature.¹¹

General procedure for the acetylation of allylic alcohols 58, 67-69 : Allylic alcohol **58/67-69** (19.6 mmol), Et₃N (5.6 mL, 40.2 mmol) and DMAP (80 mg, 0.65 mmol) were dissolved in CH₂Cl₂ (40 mL) and cooled down to 0 °C. Acetic anhydride (2.7 mL, 28.3 mmol) was added dropwise, after which the mixture was allowed to reach rt. After 1.5 hour the reaction was quenched with aq. NH₄Cl (50% sat, 40 mL), and the mixture was extracted with CH₂Cl₂ (3 x 20 mL). The organic layer was washed with sat. aq. NH₄Cl (40 mL), brine (40 mL), and sat. aq. NaHCO₃ (40 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel (5 to 10% EtOAc – Petroleum ether) to afford pure acetate **59** as an oil.

(E)-3-(4-Chlorophenyl)allyl acetate 59 : 3.4 g (82%). Spectral data was in agreement with literature.¹²

(±)-1-(4-Chlorophenyl)but-3-en-2-yl acetate 70 : 1.98 g (87%). ¹H NMR (400 MHz, CDCl₃): δ 7.26–7.23 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 5.82–5.74 (m, 1H), 5.44–5.39 (m, 1H), 5.22–5.15 (m, 2H), 2.92 (ABX system, *J* = 13.9, 7.3 Hz, 1H), 2.85 (ABX system, *J* = 13.9, 6.2 Hz, 1H), 2.01 (s, 3H) ppm.

(±)-1-Phenylbut-3-en-2-yl acetate 71 : 300 mg (65%). ¹H NMR: δ = 7.30–7.27 (m, 2H), 7.23–7.19 (m, 3H), 5.81 (ddd, *J* = 17.0, 10.5, 6.4 Hz, 1H), 5.46 (q, *J* = 6.4 Hz, 1H), 5.2 (d, *J* = 17 Hz, 1H), 5.15 (d, *J* = 10.5 Hz, 1H), 2.96 (ABX system, *J* = 13.8, 7.3 Hz, 1H), 2.88 (ABX system, *J* = 13.8, 6.2 Hz, 1H), 2.01 (s, 3H) ppm.

(±)-5-(4-Chlorophenyl)pent-1-en-3-yl acetate 72 : 1.60 g (71%). ¹H NMR (400 MHz, CDCl₃): δ 7.26–7.23 (m, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 5.84–5.75 (m, 1H), 5.28–5.19 (m, 3H), 2.64–2.59 (m, 2H), 2.07 (s, 3H), 1.99–1.84 (m, 2H).

¹⁰ P. C. Montevicchi, M. L. Navacchia *J. Org. Chem.* **1998**, *63*, 537-542.

¹¹ A. B. Charette, C. Molinaro, C. Brochu *J. Am. Chem. Soc.* **2001**, *123*, 12168-12175.

¹² Y. Su, N. Jiao *Org. Lett.* **2009**, *11*, 2980-2983.

General procedure for the allylic amination of acetate 59 : In a test tube were added PdCl₂ (9 mg, 0.05 mmol), TBAB (322 mg, 1 mmol), K₂CO₃ (276 mg, 2 mmol), followed by toluene (3 mL), **59** (210 mg, 1 mmol) and *N*-alkyl-*N*-ethylamine (1 mmol). The tube was sealed and the mixture was heated at 85 °C for 12 hours, upon which it was filtered, and the filter was rinsed with EtOAc (10 mL). The mixture was washed with water (5 mL), brine (5 mL) and dried over MgSO₄. The volatiles were removed *in vacuo* and the residue was purified by flash chromatography on silica gel (20% EtOAc – Petroleum ether) to afford allylic amine **60/61** as an oil.

(E)-N-(3-(4-Chlorophenyl)allyl)-N-ethylbutan-1-amine 60 : 204 mg (81%). ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.25 (m, 4H), 6.46 (d, *J* = 16 Hz, 1H), 6.26 (dt, *J* = 16, 6.8 Hz, 1H), 3.23 (dd, *J* = 6.8, 1.2 Hz, 2H), 2.56 (q, *J* = 7.2 Hz, 2H), 2.48–2.44 (m, 2H), 1.50–1.43 (m, 2H), 1.36–1.26 (m, 2H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 135.9, 133.0, 130.9, 128.8, 127.6, 56.2, 53.1, 47.5, 29.2, 20.9, 14.2, 11.8 ppm; HRMS (ESI) : *m/z* [*M* + H]⁺ calcd for C₁₅H₂₃ClN : 252.1514, found : 252.1513; HPLC *t*_R = 13.4 min.

(E)-N-(3-(4-Chlorophenyl)allyl)-N-ethylheptan-1-amine 61 : 1.12 g (76%). ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.22 (m, 4H), 6.43 (d, *J* = 16 Hz, 1H), 6.23 (dt, *J* = 16, 6.8 Hz, 1H), 3.20 (dd, *J* = 6.8, 1.2 Hz, 2H), 2.53 (q, *J* = 7.2 Hz, 2H), 2.44–2.40 (m, 2H), 1.46–1.43 (m, 2H), 1.25 (br s, 8H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.85 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 135.9, 132.9, 130.8, 128.9, 128.8, 127.5, 56.2, 53.5, 47.5, 32.0, 29.4, 27.7, 27.1, 22.8, 14.2, 11.9 ppm; HRMS (ESI) : *m/z* [*M* + H]⁺ calcd for C₁₈H₂₉ClN : 294.1983, found : 294.1983; HPLC *t*_R = 14.6 min.

2-(4-Chlorophenyl)acetaldehyde 64 : 4-Chlorophenethylalcohol **63** (2.7 mL, 20 mmol) was dissolved in CH₂Cl₂ (40 mL), and the reaction mixture was cooled down to 0 °C. Dess-Martin reagent (11.0 g, 26 mmol) was added and after 1 hour the reaction was quenched with 1:1 sat. aq. Na₂S₂O₃ : sat. aq. NaHCO₃ (4 mL) and the mixture was stirred for another 30 min. After filtration of the salt, the mixture was washed with brine (20 mL), the organic layer was dried with Na₂SO₄, filtered and concentrated *in vacuo*. The obtained product was used in the next step without further purification.

3-(4-Chlorophenyl)propanal 66 : 4-Chloro-iodobenzene **2** (4.78 g, 20 mmol), Pd(OAc)₂ (90 mg, 0.4 mmol), NaHCO₃ (4.2 g, 50 mmol) and NBu₄Cl (5.85 g, 20 mmol) were dissolved in DMF (130 mL). Allylic alcohol **62** (2.05 mL, 30 mmol) was added and the mixture was placed at 25 °C. After 36 hours, H₂O (130 mL) was added, the mixture was extracted with Et₂O (3 x 80 mL), washed with brine (120 mL) and H₂O (120 mL), dried over MgSO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography (5 to 20% EtOAc – Petroleum ether), yielding the **66** as a light yellow oil (1.59 g, 47%). Spectral data was in agreement with literature.¹³

General procedure for the vinylation of aldehydes 64-66 : Aldehydes **64-66** (25 mmol) were dissolved in anhydrous THF (100 mL) and the mixture was cooled down to –10 °C. Vinylmagnesiumbromide (1M solution in THF, 30 mL, 30 mmol) was added dropwise, before the mixture was allowed to reach r.t.. After 1.5 hour the reaction mixture was quenched with NH₄Cl (200 mL) and the product was extracted with Et₂O (3 x 70 mL). The organic layer was washed with brine (100 mL), dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (10 to 20% EtOAc – Petroleum ether) to afford pure allylic alcohols **67-69** as oils.

¹³ M. Yus, J. Gomis *Eur. J. Org. Chem.* **2002**, 1989-1995.

(±)-1-(4-Chlorophenyl)but-3-en-2-ol 67 : 1.85 g (51%). ¹H NMR (400 MHz, CDCl₃): δ 7.32–7.11 (m, 4H), 5.94–5.86 (m, 1H), 5.25–5.11 (m, 2H), 4.32 (dd, *J* = 12.4, 6.4 Hz, 1H), 2.86–2.74 (m, 2H), 1.60–1.57 (m, 1H) ppm.

(±)-1-phenylbut-3-en-2-ol 68 : 3.28 g (89%). Spectral data was in agreement with literature.¹⁴

(±)-5-(4-Chlorophenyl)pent-1-en-3-ol 69 : 1.86 g (100%). ¹H NMR (400 MHz, CDCl₃): δ 7.26–7.23 (m, 2H), 7.14–7.12 (m, 2H), 5.94–5.85 (m, 1H), 5.27–5.13 (m, 2H), 4.15–4.09 (m, 1H), 2.74–2.62 (m, 2H), 1.86–1.79 (m, 2H), 1.55 (s, 1H) ppm.

General procedure for the allylic amination of allylic acetates 70-72 : allylic acetates **70-72** (1 mmol) were put in a microwave tube, together with K₂CO₃ (276 mg, 2 mmol), PPh₃ (40 mg, 0.15 mmol) and Pd(OAc)₂ (12 mg, 0.05 mmol), dissolved in THF (4 mL). The corresponding amine (2 mmol) was added and the mixture was left stirring at 65°C until TLC showed completion (2-18 hours). When completed, the mixture was filtered on paper filter and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel (20 to 100% EtOAc – Petroleum ether) to afford pure allylamines **73-78**.

(E)-N-Butyl-4-(4-chlorophenyl)-N-ethylbut-2-en-1-amine 73 : 159 mg (60%). ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J* = 7.6 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 5.72–5.65 (m, 1H), 5.61–5.54 (m, 1H), 3.33 (d, *J* = 6.4 Hz, 2H), 3.07 (d, *J* = 6.4 Hz, 2H), 2.52 (dd, *J* = 14.0, 6.8 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 1.46–1.39 (m, 2H), 1.33–1.19 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 139.0, 131.8, 131.5, 129.9, 129.3, 128.7, 128.5, 127.5, 55.6, 52.8, 47.2, 38.3, 29.0, 20.8, 14.1, 11.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₆H₂₅ClN : 266.1670, found : 266.1670; HPLC *t*_R = 13.3 min.

(E)-N-(4-(4-Chlorophenyl)but-2-en-1-yl)-N-ethylheptan-1-amine 74 : 654 mg (42%). ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J* = 2.0 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 5.76–5.68 (m, 1H), 5.61–5.54 (m, 1H), 3.33 (d, *J* = 6.8 Hz, 2H), 3.06 (d, *J* = 6.0 Hz, 2H), 2.51 (q, *J* = 7.2 Hz, 2H), 2.40 (t, *J* = 7.6 Hz, 2H), 1.47–1.38 (m, 2H), 1.30–1.22 (m, 8H), 1.03 (t, *J* = 9.6 Hz, 3H), 0.88 (t, *J* = 6.4 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 138.8, 131.6, 131.3, 130.7, 129.7, 129.2, 128.6, 128.3, 55.4, 53.0, 47.1, 38.1, 31.8, 29.2, 27.5, 26.7, 22.6, 14.0, 11.6 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₉H₃₁ClN : 308.2140, found : 308.2141; HPLC *t*_R = 14.5 min.

(E)-N-Butyl-N-ethyl-4-phenylbut-2-en-1-amine 75 : 315 mg (68%). ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.25 (m, 2H), 7.20–7.16 (m, 3H), 5.76–5.69 (m, 1H), 5.62–5.55 (m, 1H), 3.37 (d, *J* = 6.8 Hz, 2H), 3.07 (d, *J* = 6.8 Hz, 2H), 2.52 (q, *J* = 7.2 Hz, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 1.46–1.39 (m, 2H), 1.33–1.22 (m, 2H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 140.7, 132.2, 128.9, 128.6, 128.5, 126.1, 55.7, 52.9, 47.3, 39.1, 29.1, 20.9, 14.2, 11.8 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₆H₂₆N : 232.2060, found : 232.2059; HPLC *t*_R = 13.1 min.

(E)-N-Ethyl-N-(4-phenylbut-2-en-1-yl)heptan-1-amine 76 : 173 mg (64%). ¹H NMR (400 MHz, CDCl₃) δ 7.25 (d, *J* = 3.2 Hz, 2H), 7.17 (d, *J* = 7.6 Hz, 2H), 5.77–5.70 (m, 1H), 5.63–5.56 (m, 1H), 3.37 (d, *J* = 6.4 Hz, 2H), 3.09 (d, *J* = 6.8 Hz, 2H), 2.54 (q, *J* = 14.4, 7.2 Hz, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 1.48–1.43 (m, 2H), 1.31–1.20 (m, 8H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 4.8 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 140.6, 132.4, 128.6, 128.5, 126.1, 55.6, 53.1, 47.2, 39.0, 32.0, 29.4, 27.7, 26.8, 22.7, 14.2, 11.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₉H₃₂N : 274.2529, found : 274.2529; HPLC *t*_R = 14.2 min.

¹⁴ R. E. Kyne, M. C. Ryan, L. T. Kliman, J. P. Morken *Org. Lett.* **2010**, *12*, 3796-3799.

(E)-N-Butyl-5-(4-chlorophenyl)-N-ethylpent-2-en-1-amine 77 : 197 mg (70%). ¹H NMR (400 MHz, CDCl₃) δ 7.22 (dd, *J* = 6.8, 4.8 Hz, 2H), 7.11 (dd, *J* = 14.0, 8.4 Hz, 2H), 5.59–5.45 (m, 2H), 3.00 (d, *J* = 6.0 Hz, 2H), 2.65 (q, *J* = 14.8, 7.2 Hz, 2H), 2.45–2.41 (m, 2H), 2.37–2.30 (m, 4H), 1.44–1.36 (m, 2H), 1.34–1.23 (m, 2H), 1.04 (t, *J* = 7.2 Hz, 3H), 0.99 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 140.4, 132.2, 131.6, 129.9, 128.5, 55.8, 52.8, 47.1, 35.2, 34.1, 29.1, 20.9, 14.2, 11.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₇H₂₇ClN : 280.1827, found : 280.1826; HPLC *t*_R = 14.2 min.

(E)-N-(5-(4-Chlorophenyl)pent-2-en-1-yl)-N-ethylheptan-1-amine 78 : 261 mg (81%). ¹H NMR (400 MHz, CDCl₃) δ 7.22 (dd, *J* = 6.4, 2.0 Hz, 2H), 7.11 (dd, *J* = 14.0, 8.8 Hz, 2H), 5.59–5.45 (m, 2H), 3.00 (d, *J* = 6.0 Hz, 2H), 2.65 (q, *J* = 7.2 Hz, 2H), 2.45–2.40 (m, 2H), 2.38–2.30 (m, 4H), 1.45–1.37 (m, 2H), 1.34–1.20 (m, 8H), 0.99 (t, *J* = 7.2 Hz, 3H), 0.90 (t, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 140.4, 132.2, 131.6, 129.9, 128.5, 55.8, 53.1, 47.1, 35.2, 34.1, 32.0, 29.5, 27.8, 27.0, 22.8, 14.3, 11.7 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₂₀H₃₃ClN : 322.2295, found : 322.2296; HPLC *t*_R = 13.6 min.

(Z)-N-Ethyl-N-(4-phenylbut-2-en-1-yl)heptan-1-amine 79 : Propargylic amine **21** (136 mg, 0.5 mmol), quinoline (10 μL, 0.08 mmol) and Lindlar's catalyst (20% w/w Pd, 49 mg, 2.5 mg Pd) were dissolved in EtOAc (140 mL). The flask was flushed with N₂ before being saturated with H₂. After 72 hours the mixture was concentrated *in vacuo*. The residue was purified by 2 x Preparative TLC (30% EtOAc – Petroleum ether and 5% MeOH – CH₂Cl₂), yielding **79** (53 mg, 25%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.28 (d, *J* = 6.8 Hz, 2H), 7.18 (d, *J* = 7.2 Hz, 2H), 5.75–5.69 (m, 1H), 5.66–5.60 (m, 1H), 3.44 (d, *J* = 6.8 Hz, 2H), 3.23 (d, 6.4 Hz, 2H), 2.57 (q, *J* = 14.0, 6.8 Hz, 2H), 2.45 (t, *J* = 7.6 Hz, 2H), 1.47 (m, 2H), 1.27–1.26 (m, 8H), 1.05 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 5.6 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 140.8, 130.7, 128.6, 128.4, 128.1, 126.1, 53.4, 50.2, 47.5, 33.9, 32.0, 29.8, 29.4, 27.8, 27.0, 22.8, 14.3, 11.9 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₉H₃₂N : 274.2528, found : 274.2529; HPLC *t*_R = 14.2 min.

(E)-N-(4-(4-Chlorophenyl)but-2-en-1-yl)-N,N-diethylheptan-1-aminium iodide 80 : Allylamine **78** (100 mg, 0.32 mmol) was dissolved in acetone (1.1 mL). Ethyliodide (40 μL, 0.48 mmol) was added. After 24 hours of stirring an additional amount of ethyliodide (40 μL, 0.48 mmol) was added and after another 24 hours the reaction mixture was heated to 55 °C. After 4 days in total the mixture was concentrated *in vacuo*. The residue was dissolved in CH₃CN and then precipitated by adding Et₂O. After filtration and removal of the solvents, ammonium **80** (89 mg, 60%) was obtained as a dark brown oil. ¹H NMR (400 MHz, CDCl₃) δ 7.27 (d, *J* = 6.8 Hz, 2H), 7.15 (d, *J* = 8.4 Hz, 2H), 6.39–6.32 (m, 1H), 5.72–5.64 (m, 1H), 4.04 (d, *J* = 7.6 Hz, 2H), 3.55–3.40 (m, 6H), 3.21 (t, *J* = 8.4 Hz, 2H), 1.71–1.69 (m, 2H), 1.39 (t, *J* = 7.2 Hz, 7H), 1.30–1.19 (m, 9H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 144.3, 136.7, 130.2, 128.9, 116.9, 60.2, 58.0, 54.0, 38.3, 31.6, 28.8, 26.4, 22.5, 22.3, 14.1, 8.5 ppm; HRMS (ESI) : *m/z* [*M*]⁺ calcd for C₂₁H₃₅Cl : 336.2453, found : 336.2453; HPLC *t*_R = 14.3 min.

N-Ethyl-N-(4-phenylbutyl)heptan-1-amine 81 : Allylamine **78** (180 mg, 0.6 mmol) and Pd/C (10% w/w Pd, 55 mg, 30 wt%) were dissolved in MeOH (10 mL). The flask was flushed with N₂ before being saturated with H₂. After 4.5 hours stirring at r.t., the mixture was filtered on Celite, the volatiles were removed *in vacuo* and the residue was purified by flash chromatography on silica gel (100% EtOAc then 20% MeOH – CH₂Cl₂) to afford **81** (53 mg, 34%) as an oil. ¹H NMR (400 MHz, CDCl₃) δ 7.29 (t, *J* = 8.4 Hz, 2H), 7.17 (t, *J* = 8.4 Hz, 2H), 3.03 (q, *J* = 14.8, 7.2 Hz, 2H), 2.94–2.86 (m, 4H), 2.67 (t, *J* = 7.6 Hz, 2H), 1.84–1.77 (m, 2H), 1.73–1.65 (m, 4H), 1.40–1.27 (m, 11H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 141.2, 128.5, 128.3, 126.1, 51.7, 51.6, 47.0, 35.1, 31.6, 28.7, 28.6, 26.8, 23.3, 23.0, 22.5, 14.0, 8.9 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₉H₃₄N : 276.2685, found : 276.2686; HPLC *t*_R = 14.5 min.

Methyl 5-(4-chlorophenyl)-5-oxopentanoate 84 : Chlorobenzene **82** (2 mL, 20 mmol) and ethyl(4-chloroformyl)butyrate **83** (3.4 mL, 22 mmol) were added to AlCl₃ (5.33 g, 40 mmol) in 1,2-dichloroethane (25 mL). After 15 hours of stirring at r.t., the mixture was poured into 37% conc. HCl (40 mL), and the mixture was extracted with CHCl₃ (3 x 20 mL), dried over MgSO₄, and concentrated *in vacuo*. The residue was purified by column chromatography (10 to 20% EtOAc – Petroleum ether) to afford **84** (3.5 g, 69%) as a dark orange oil. Spectral data was in agreement with literature.¹⁵

General procedure for the reduction of ester 84 and acid 85 : 3-(4-chlorobenzoyl)propionic acid **85** or ester **84** (40 mmol) and KOH (5.9 g, 105 mmol) were dissolved in diethylene glycol (40 mL). Hydrazine monohydrate (4.2 mL, 52 mmol) was added and the flask was placed at 150°C with a drying tube on top containing anhydrous CaCl₂. After overnight stirring, the temperature was raised to 170°C and after 4 additional hours the mixture was cooled down, diluted with H₂O (40 mL), and poured into aq. HCl (2.5M, 50 mL). The mixture was filtered, and the precipitate was purified by flash chromatography on silica gel (40% EtOAc – Petroleum ether) to afford acids **86-87**.

4-(4-Chlorophenyl)butanoic acid 86 : 6.9 g (87%). Spectral data was in agreement with literature.¹⁶

5-(4-Chlorophenyl)pentanoic acid 87 : 2.2 g (73%). Spectral data was in agreement with literature.¹⁷

General procedure for the synthesis of amines 90-92 from esters 88-89 : Esters **88-89** (1 mmol) were dissolved in CH₂Cl₂ (2 mL) and cooled to -78°C. DiBAL-H (1.2M in toluene, 1 mL, 1.2 mmol) was added dropwise, and after 2 hours H₂O (4 mL) and CH₂Cl₂ (4 mL) were added. After an additional 30 min of stirring at r.t., the mixture was extracted with CH₂Cl₂ (3 x 4 mL), washed with H₂O (5 mL) and brine (5 mL), and the organic layers were dried over MgSO₄, filtered and concentrated *in vacuo*. The resulting crude aldehyde (~1 mmol) and NaBH(OAc)₃ (318 mg, 1.5 mmol) were dissolved in 1,2-dichloroethane (10 mL), and the corresponding amine (1.1 mmol) was added. After overnight stirring sat. aq. NaHCO₃ (10 mL) was added and the mixture was extracted with CH₂Cl₂ (3 x 10 mL), the organic layer was dried over Na₂SO₄, filtered and concentrated *in vacuo*. The residue was purified by preparative TLC (EtOAc) to afford amines **90-92** as oils.

N-(4-(4-Chlorophenyl)butyl)-N-ethylheptan-1-amine 90 : 227 mg (73%). ¹H NMR (400 MHz, CDCl₃) δ 7.22 (d, *J* = 8.0 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 2.58 (t, *J* = 7.6 Hz, 2H), 2.51 (q, *J* = 7.2 Hz, 2H), 2.45–2.37 (m, 4H), 1.62–1.55 (m, 2H), 1.51–1.40 (m, 4H), 1.30–1.27 (m, 8H), 1.01 (t, *J* = 6.8 Hz, 3H), 0.88 (t, *J* = 6.4 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 141.0, 131.4, 129.8, 128.4, 127.2, 53.5, 53.3, 47.5, 35.2, 31.9, 29.4, 29.4, 27.7, 26.9, 26.5, 22.7, 14.2, 11.6 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₉H₃₃ClN : 310.2297, found : 310.2296; HPLC *t*_R = 14.9 min.

N-Butyl-5-(4-chlorophenyl)-N-ethylpentan-1-amine 91 : 113 mg (40%). ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.0 Hz, 2H), 2.59–2.52 (m, 4H), 2.45–2.40 (m, 4H), 1.64–1.57 (m, 2H), 1.52–1.39 (m, 4H), 1.34–1.26 (m, 4H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.91 (t, *J* = 7.6 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 141.2, 131.4, 129.8, 128.4, 128.3, 53.3, 53.1, 47.4, 35.3, 31.4, 28.9, 26.7, 20.9, 14.2, 11.5 ppm; HRMS (ESI) : *m/z* [*M* + *H*]⁺ calcd for C₁₇H₂₉ClN : 282.1983, found : 282.1983; HPLC *t*_R = 14.0 min.

¹⁵ K. Itoh, S. Nakanishi, Y. Otsuji *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2965-2977.

¹⁶ T. Ohishi, L. Zhang, M. Nishiura, Z. Hou *Angew. Chem. Int. Ed.* **2011**, *50*, 8264-8267.

¹⁷ E. Shirakawa, D. Ikeda, S. Masui, M. Yoshida, T. Hayashi *J. Am. Chem. Soc.* **2012**, *134*, 272-279.

***N*-(5-(4-Chlorophenyl)pentyl)-*N*-ethylheptan-1-amine 92** : 168 mg (52%). ¹H NMR (400 MHz, CDCl₃) δ 7.23 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 2.56 (m, 4H), 2.44 (t, *J* = 7.6 Hz, 4H), 1.64–1.57 (m, 2H), 1.52–1.43 (m, 4H), 1.34–1.28 (m, 10H), 1.03 (t, *J* = 7.2 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 141.1, 131.4, 129.8, 128.4, 128.3, 53.4, 53.3, 47.4, 35.3, 31.9, 31.4, 29.4, 27.7, 27.2, 26.6, 26.5, 22.7, 14.2, 11.4 ppm; HRMS (ESI) : *m/z* [*M* + H]⁺ calcd for C₂₀H₃₅ClN : 324.2453, found : 324.2453; HPLC *t*_R = 15.3 min.

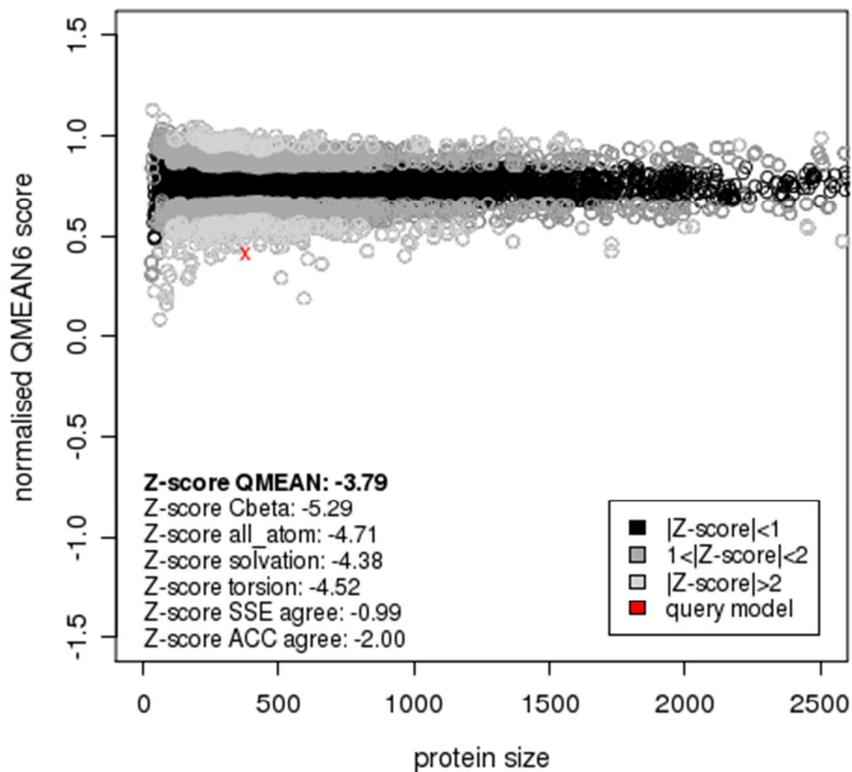
General procedure for the alkylation of piperidines 93 and 94 : to a solution piperidine (2 mmol), K₂CO₃ (720 mg, 5.2 mmol), NaI (140 mg, 0.9 mmol) in acetone (10 mL) was added *n*-bromoheptane (350 μL, 2.2 mmol). The mixture was refluxed for 15 hours, upon which the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel (EtOAc) to afford piperidines **95** and **96** as oils.

4-Benzyl-1-heptylpiperidine 95 : 488 mg (89%). ¹H NMR (400 MHz, CDCl₃) δ 7.27–7.23 (m, 2H), 7.18–7.11 (m, 3H), 2.89 (d, *J* = 11.6 Hz, 2H), 2.52 (d, *J* = 7.2 Hz, 2H), 2.28–2.24 (m, 2H), 1.81 (td, *J* = 6.0, 2.0 Hz, 2H), 1.61 (d, *J* = 12.4 Hz, 8H), 1.51–1.44 (m, 3H), 1.28–1.24 (m, 10H), 0.86 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 140.9, 129.2, 128.2, 125.8, 59.4, 54.3, 54.1, 43.4, 38.1, 32.3, 31.9, 29.4, 27.8, 27.2, 22.7, 14.2 ppm; HRMS (ESI) : *m/z* [*M* + H]⁺ calcd for C₁₉H₃₃N : 274.2529, found : 274.2530; HPLC *t*_R = 15.0 min.

(1-Heptylpiperidin-4-yl)(phenyl)methanone 96 : 2330 mg (40%). ¹H NMR (400 MHz, CDCl₃) δ 7.94 (d, *J* = 7.6 Hz, 2H), 7.55–7.53 (m, 1H), 7.47–7.43 (m, 2H), 3.42–3.39 (m, 1H), 3.10 (d, *J* = 11.6 Hz, 2H), 2.50 (t, *J* = 8.0 Hz, 2H), 2.45–2.33 (m, 2H), 1.98–1.95 (m, 4H), 1.59 (br s, 2H), 1.30–1.28 (m, 8H), 0.88 (t, *J* = 7.2 Hz, 3H) ppm; ¹³C NMR (101 MHz, CDCl₃) δ 202.1, 135.7, 132.9, 128.9, 128.5, 128.1, 60.2, 58.5, 52.6, 42.6, 31.6, 29.0, 27.9, 27.5, 27.3, 26.2, 22.4, 13.9 ppm; HRMS (ESI) : *m/z* [*M* + H]⁺ calcd for C₁₉H₃₀NO : 288.2322, found : 288.2322; HPLC *t*_R = 13.4 min.

Statistical analysis of homology model using swiss-model¹⁸

Comparison with non-redundant set of PISA assemblies



¹⁸ http://swissmodel.expasy.org/workspace/index.php?func=tools_structureassessment1