



J. Serb. Chem. Soc. 90 (5) S140–S200 (2025)

SUPPLEMENTARY MATERIAL TO
Hybrids of 4-aminoquinolines and adamantane as inhibitors of AChE

KATARINA KOMATOVIĆ¹, ANA MATOŠEVIĆ², MARIO ZLATOVIĆ¹,
DUŠAN SLADIĆ¹, ANITA BOSAK² and DEJAN M. OPSENICA^{3,4*}

¹University of Belgrade, Faculty of Chemistry, Studentski trg 12–16, 11158 Belgrade, Serbia,

²Institute for Medical Research and Occupational Health, Ksaverska cesta 2, 10001 Zagreb, Croatia, ³Institute of Chemistry Technology and Metallurgy, University of Belgrade, Njegoševa 12, 11000 Beograd, Serbia and ⁴Centre of Excellence in Environmental Chemistry and Engineering, ICTM, 11000 Belgrade, Serbia

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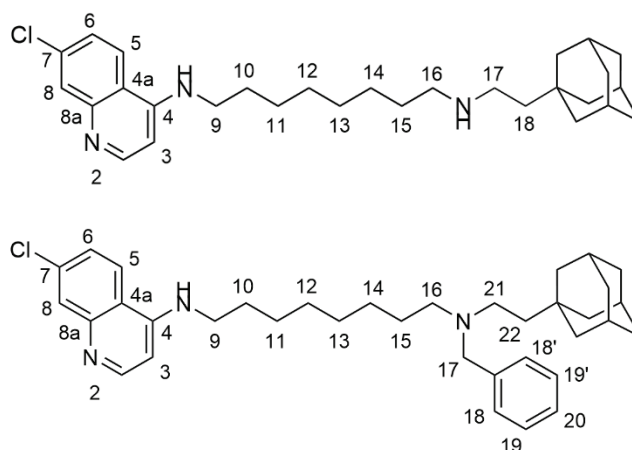
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* Corresponding author. E-mail: dejan.opsenica@ihtm.bg.ac.rs

1. SYNTHESIS

1.1. Synthetic procedures and spectral data

Numeration method:



*N*¹-Benzyl-*N*⁸-(7-chloroquinolin-4-yl)octane-1,8-diamine (**2**).

Compound **2** was synthesized according to the published procedure.¹ Yield 84,1 mg (74%), pale yellow solid, Mp = 61-65 °C. IR (ATR): 3315m, 2927s, 2852s, 1580s, 1452m, 1367m, 1241m, 1212m, 1158m, 1134m, 1081m, 1026w, 899w, 875w, 850w, 804m, 754m, 697m, 598w, 525w cm⁻¹. ¹H NMR (400 MHz, CD₃OD, δ): 8.32 (d, *J* = 5.7 Hz, 1H, H-2), 8.11 (d, *J* = 9.0 Hz, 1H, H-5), 7.76 (d, *J* = 2.1 Hz, 1H, H-8), 7.44 – 7.38 (m, 6H, H-6 and H-18-20), 6.53 (d, *J* = 5.8 Hz, 1H, H-3), 4.08 (s, 2H, H-17), 3.37 (t, *J* = 7.2 Hz, 2H, H-9), 2.94 – 2.87 (m, 2H, H-16), 1.74 (quint, *J* = 7.2 Hz, 2H, H-10), 1.69 – 1.58 (m, 2H, H-15), 1.49 – 1.34 (m, 8H, 4× -CH₂, H-(11-14)).

*N*¹-(2-(Adamantan-1-yl)ethyl)-*N*¹-benzyl-*N*⁸-(7-chloroquinolin-4-yl)octane-1,8-diamine (**5**).

Into the solution of **2** (18.3 mg, 0.0462 mmol) and 1-adamantaneacetaldehyde (16.5 mg, 0.0926 mmol) in DCE (1,5 mL), NaBH(OAc)₃ (29.4 mg, 0.1387 mmol) was added. The mixture was stirred at room temperature for 2 h, in an Ar atmosphere. The reaction was quenched with sat. aqueous solution of NaHCO₃, transferred into a separatory funnel and the aqueous layer was extracted three times with DCM. The organic layers were combined, washed with brine and dried over anhyd. Na₂SO₄. The solvent was evaporated and the product was isolated after chromatographic purification (preparative thin-layer chromatography, silica gel, DCM/MeOH). Yield 20.2 mg (78%), dark yellow oil. IR (ATR): 3263w, 3062w, 3026w, 2904s, 2847s, 1611m, 1580s, 1540m, 1492w, 1451m, 1368m, 1332m, 1281w, 1249w, 1203w, 1136w, 1101w, 1080w, 1028w, 968w, 902w, 877w, 852w, 806w, 768w, 737m, 699w, 645w, 623w, 430w cm⁻¹. ¹H NMR (400 MHz, CDCl₃, δ) 8.51 (d, *J* = 5.4 Hz, 1H, H-2), 7.95 (s, 1H, H-8), 7.68 (d, *J* = 9.0 Hz, 1H, H-5), 7.38 – 7.18 (m, 6H, H-6, H-18, H-18', H-19, H-19' and H-20), 6.39 (d, *J* = 5.4 Hz, 1H, H-3), 5.14 (s, 1H, -NH), 3.57 (s, 2H, H-17), 3.29 (q, *J* = 6.5 Hz, 2H, H-9), 2.51 – 2.37 (m, 4H, H-16 and H-21), 1.90 (s, 3H, 3× -CH(Ad)), 1.78 – 1.56 (m, 8H, 3× -CH₂(Ad) and -CH₂ H-10), 1.50 – 1.25 (m, 18H, 3× -CH₂(Ad) and 6× -CH₂ H-(11-15) and H-22). ¹³C NMR (100 MHz, CDCl₃, δ) 151.91, 149.97, 148.97, 139.54, 135.00, 129.09, 128.68, 128.22, 126.90, 125.36, 121.10, 117.18, 99.12, 58.43, 53.69, 47.57, 43.39, 42.64, 40.43, 37.28, 31.99, 29.51,

29.41, 28.95, 28.78, 27.42, 27.19, 26.92. ESI-HRMS (*m/z*): calc. for $[C_{36}H_{48}ClN_3+H]^+$ 558.3610, found 558.3611.

*N*¹-(7-Chloroquinolin-4-yl)octane-1,8-diamine (9).

Compound **9** was synthesized according to the published procedure.² Yield 2,6513 g (78%), pale yellow solid, Mp = 104–108 °C. IR (ATR): 3324m, 3260m, 3175m, 2928s, 2851s, 1612m, 1576s, 1536m, 1476m, 1463m, 1450m, 1428m, 1391m, 1369m, 1328m, 1281w, 1251w, 1218w, 1199w, 1166w, 1133m, 1079w, 1026w, 981w, 954w, 925w, 903w, 875w, 853m, 812m, 796w, 770w, 727w, 648w, 622w, 597w, 527w, 495w, 441w cm⁻¹. ¹H NMR (400 MHz, CD₃OD, δ): 8.33 (d, *J* = 5.6 Hz, 1H, H-2), 8.08 (d, *J* = 9.0 Hz, 1H, H-5), 7.76 (s, 1H, H-8), 7.40 – 7.34 (m, 1H, H-6), 6.47 (d, *J* = 5.7 Hz, 1H, H-3), 3.35 – 3.28 (m, 2H, H-9, overlapped with CD₃OD), 2.61 (t, *J* = 7.2 Hz, 2H, H-16), 1.73 (quint, *J* = 7.3 Hz, 2H, H-10), 1.51 – 1.28 (m, 10H, 5 × -CH₂).

*N*¹-((Adamantan-1-yl)methyl)-*N*⁸-(7-chloroquinolin-4-yl)octane-1,8-diamine (1).

Compound **1** was synthesized according to the published procedure.³ Yield 395.3 mg (26 %), yellow oil. IR (ATR): 3277m, 3064w, 2905s, 2849s, 1610m, 1581s, 1541w, 1453m, 1368w, 1332m, 1282w, 1250w, 1137w, 878w, 851w, 806w. ¹H NMR (400 MHz, CD₃OD, δ) 8.33 (d, *J* = 5.6 Hz, 1H, H-2), 8.10 (d, *J* = 9.0 Hz, 1H, H-5), 7.76 (d, *J* = 1.4 Hz, 1H, H-8), 7.38 (dd, *J*₁ = 9.0 Hz, *J*₂ = 1.8 Hz, 1H, H-6), 6.49 (d, *J* = 5.6 Hz, 1H, H-3), 3.35–3.34 (m, 2H, H-9 overlapped with MeOH solvent), 2.68 – 2.60 (m, 2H, H-16), 2.35 (s, 2H, H-17), 2.00 – 1.93 (m, 3H, 3 × -CH(Ad)), 1.81 – 1.63 (m, 8H, 3 × -CH₂(Ad) and -CH₂ H-10), 1.61 – 1.30 (m, 16H, 3 × -CH₂(Ad) and 5 × -CH₂).

*N*¹-((Adamantan-1-yl)methyl)-*N*¹-benzyl-*N*⁸-(7-chloroquinolin-4-yl)octane-1,8-diamine (4).

Into the solution of **1** (64 mg, 0.1409 mmol) and benzaldehyde (30 μL, 0.2954 mmol) in dry MeOH (1.7 mL), the mixture of NaBH₃CN (9.7 mg, 0.1544 mmol) and ZnCl₂ (9.6 mg, 0.0704 mmol) in dry MeOH (1.7 mL) was added. After stirring the reaction mixture at room temperature for 24 h, the solvent was evaporated under reduced pressure. Sat. aqueous solution of NaHCO₃ and DCM were added, the mixture was transferred into a separatory funnel and layers were separated. The water layer was extracted with DCM and combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated and the product was isolated after chromatographic purification (dry-flash chromatography, silica gel, gradient Hex/EA, then preparative thin-layer chromatography, silica gel, EA/MeOH, then dry-flash chromatography, silica gel, gradient DCM/MeOH). Yield 20.7 mg (27%), yellow oil. IR (ATR): 3261w, 3062w, 3026w, 2904s, 2848s, 1611m, 1581s, 1540m, 1492w, 1452m, 1368m, 1332m, 1282w, 1247w, 1205w, 1137w, 1100w, 1081w, 1028w, 983w, 902w, 877w, 852w, 806w, 768w, 736w, 698w, 645w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ) 8.51 – 8.46 (m, 1H, H-2), 7.95 (d, *J* = 1.9 Hz, 1H, H-8), 7.68 (dd, *J*₁ = 9.0 Hz, *J*₂ = 3.3 Hz, 1H, H-5), 7.38 (d, *J* = 7.3 Hz, 2H, H-18 and H-18'), 7.36 – 7.32 (m, 1H, H-6), 7.29 (t, *J* = 7.5 Hz, 2H, H-19 and H-19'), 7.21 (t, *J* = 7.3 Hz, 1H, H-20), 6.38 (dd, *J*₁ = 5.4 Hz, *J*₂ = 1.9 Hz, 1H, H-3), 5.33 – 5.17 (m, 1H, Ar-NH), 3.58 (s, 2H, H-17), 3.28 (q, *J* = 7.1 Hz, 2H, H-9), 2.34 – 2.26 (m, 2H, H-16), 2.13 (s, 2H, H-21), 1.97 – 1.90 (m, 3H, 3 × -CH(Ad)), 1.76 – 1.58 (m, 8H, H-10 and 3 × -CH₂(Ad)), 1.51 (d, *J* = 2.2 Hz, 6H, 3 × -CH₂(Ad)), 1.45 – 1.37 (m, 4H, H-11 and H-15), 1.35 – 1.28 (m, 2H, H-14), 1.27 – 1.18 (m, 4H, H-12 and H-13). ¹³C NMR (125 MHz, CDCl₃, δ) 151.42, 150.25, 148.49, 141.14, 135.27, 128.68, 128.30, 128.14, 126.64, 125.51, 121.22, 117.09, 99.06, 68.21, 62.10, 56.45, 43.47, 41.60, 37.44, 35.17, 29.59, 29.45, 28.96, 28.74, 27.70, 27.37, 27.22. ESI-HRMS (*m/z*): calc. for $[C_{35}H_{46}ClN_3+H]^+$ 544.3453, found 544.3456.

*N*¹-(2-(Adamantan-1-yl)ethyl)-*N*⁸-(7-chloroquinolin-4-yl)octane-1,8-diamine (3).

Into the solution of **9** (153 mg, 0.5003 mmol) and 1-adamantaneacetaldehyde (89.2 mg, 0.5004 mmol) in DCM (11.5 mL), NaBH(OAc)₃ (212.1 mg, 1.0008 mmol) was added. After stirring the mixture for 22 h, at room temperature, the reaction was quenched with aqueous NaOH (1 M). The organic layer was separated and the aqueous layer was extracted with DCM. The combined organic layers were washed with brine and dried over anhydrous Na₂SO₄. The solvent was evaporated and the product was isolated after chromatographic purification (dry-flash chromatography, silica gel, gradient prepared from DCM and mixture [MeOH/NH₃(aq)=9/1], then multiple preparative thin-layer chromatography, silica gel, EA/MeOH/NH₃(aq)). Yield 36.4 mg (16%), pale yellow oil. IR (ATR): 3278m, 2904s, 2848s, 1611m, 1581s, 1541m, 1451m, 1428w, 1368m, 1332w, 1282w, 1203w, 1137w, 1080w, 901w, 878w, 852w, 806w, 768w, 738w, 646w cm⁻¹. ¹H NMR (400 MHz, CDCl₃, δ) 8.52 (d, *J* = 5.3 Hz, 1H, H-2), 7.95 (s, 1H, H-8), 7.67 (d, *J* = 8.9 Hz, 1H, H-5), 7.35 (d, *J* = 8.9 Hz, 1H, H-6), 6.40 (d, *J* = 5.4 Hz, 1H, H-3), 5.07 (s, 1H, Ar-NH), 3.29 (q, *J* = 6.7 Hz, 2H, H-9), 2.67 – 2.53 (m, 4H, H-16 and H-17), 1.93 (s, 3H, 3× -CH(Ad)), 1.79 – 1.58 (m, 8H, 3× -CH₂(Ad) and -CH₂ H-10), 1.54 – 1.40 (m, 10H, 3× -CH₂(Ad) and 2× -CH₂ H-15 and H-11), 1.40 – 1.24 (m, 8H, H-18 and 3× -CH₂ H-(12-14)). ¹³C NMR (100 MHz, CDCl₃, δ) 152.17, 149.83, 149.22, 134.90, 128.90, 125.32, 121.02, 117.22, 99.17, 50.33, 44.71, 44.48, 43.37, 42.75, 37.26, 31.96, 30.15, 29.55, 29.38, 28.97, 28.78, 27.44, 27.19. ESI-HRMS (*m/z*): calc. for [C₂₉H₄₂ClN₃+H]⁺ 468.3140, found 468.3141.

3-Hydroxyadamantane-1-carboxylic acid (11).⁴

1-Adamantanecarboxylic acid **10** (1 g, 5.5478 mmol) was introduced portionwise into the ice-cold mixture of 96% H₂SO₄ (4 mL) and 65% HNO₃ (0.5 mL). Then, the reaction mixture was spontaneously warmed to room temperature and stirred overnight. Water was added in drops at 10 °C and the formation of precipitate was completed after additional stirring and cooling. The product was isolated after filtration, rinsed with water and dried. Yield 970.1 mg (89%), white solid, Mp = 195–200 °C. IR (ATR): 3440s, 2949s, 2909s, 2862m, 2809m, 2640m, 1708s, 1454m, 1392w, 1341m, 1273s, 1248s, 1227m, 1193w, 1147w, 1120m, 1046w, 1018m, 978w, 941m, 915m, 883w, 724m, 670w, 564w, 524w, 439w cm⁻¹. ¹H NMR (500 MHz, CD₃OD, δ) 2.25 – 2.19 (m, 2H, 2× -CH), 1.84 – 1.74 (m, 6H, 3× -CH₂), 1.73 – 1.65 (m, 4H, 2× -CH₂), 1.64 – 1.59 (m, 2H, -CH₂). ¹³C NMR (125 MHz, CD₃OD, δ) 180.42, 68.72, 47.23, 45.05, 44.89, 39.01, 36.22, 31.71.

3-Bromoadamantane-1-carboxylic acid (12).⁵

The mixture of **11** (1.8264 g, 9.3068 mmol) and 48% HBr (18.42 mL, 162.8227 mmol) was stirred in an Ace pressure tube at 90 °C for 6 h and then cooled at 4 °C. The product was isolated after filtration, rinsed with cold water and dried. Yield 2.0389 g (84%), white solid, Mp = 140–143 °C. IR (ATR): 2918s, 2862m, 2654w, 2327w, 1690s, 1478w, 1453w, 1416w, 1329w, 1315m, 1288m, 1171w, 1148w, 1107w, 1083w, 956w, 895w, 831w, 763w, 746w, 691w, 671w, 535w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ) 2.49 (s, 2H, -CH₂), 2.37 – 2.27 (m, 4H, 2× -CH₂), 2.25 – 2.20 (m, 2H, 2× -CH), 1.91 (d, *J* = 2.9 Hz, 4H, 2× -CH₂), 1.75 – 1.67 (m, 2H, -CH₂). ¹³C NMR (125 MHz, CDCl₃, δ) 181.88, 63.29, 49.44, 48.15, 44.80, 37.01, 34.53, 31.73.

3-(Hydroxymethyl)adamantan-1-ol (13).⁶

A solution of **11** (380 mg, 1.9364 mmol), Et₃N (0.32 mL, 2.3085 mmol) and ClCOOEt (0.22 mL, 2.3007 mmol) in DCM (10 mL) was stirred at room temperature for 2 h. The reaction mixture was evaporated to dryness and the residue was dissolved in 20 mL DCM/THF = 3/1, followed by the addition of NaBH₄ (293 mg, 7.7452 mmol) and MeOH (6 mL) in small portions. After 21 h, the reaction was quenched by pouring into ice/dilute HCl mixture and layers were

separated. The organic layer was washed with sat. NaHCO_3 and brine. The aqueous layer was neutralized to pH 7, extracted twice with EA and the combined organic layers were washed with brine. Finally, both organic layers were combined and dried over anhydrous Na_2SO_4 . The solvent was evaporated and the product was isolated after chromatographic purification (dry-flash chromatography, silica gel, gradient Hex/EA). Yield 245.8 mg (70%), white crystals, $\text{Mp} = 108\text{--}112\text{ }^\circ\text{C}$. IR (ATR): 3367s, 3302s, 2912s, 2850s, 2668w, 1512w, 1454m, 1430m, 1342m, 1315m, 1249w, 1209w, 1168m, 1149m, 1112m, 1056s, 1026m, 980w, 959w, 941m, 920w, 898w, 833w, 797w, 774w, 735w, 708w, 648m, 618w, 596w, 549w, 462w, 430w cm^{-1} . ^1H NMR (500 MHz, CD_3OD , δ) 3.17 (s, 2H, $-\text{CH}_2\text{OH}$), 2.21 – 2.15 (m, 2H, 2 $-\text{CH}$), 1.72 – 1.54 (m, 6H, 3 $\times$ $-\text{CH}_2$), 1.47 – 1.39 (m, 6H, 3 $\times$ $-\text{CH}_2$). ^{13}C NMR (125 MHz, CD_3OD , δ) 72.96, 69.30, 47.50, 45.61, 39.40, 39.07, 36.89, 31.87. EI-GC/MS m/z (%): 182.1 (13) $[\text{M}]^+$, 151.1 (100) $[\text{M} - \text{CH}_2\text{OH}]^+$, 107.0 (16), 95.0 (36).

(3-Bromoadamantan-1-yl)methanol (14).⁷

A solution of **12** (2.0389 g, 7.8679 mmol), Et_3N (1.3 mL, 9.3784 mmol) and ClCOOEt (0.9 mL, 9.4069 mmol) in DCM (41.5 mL) was stirred at room temperature for 150 min. The reaction mixture was evaporated to dryness and the residue was dissolved in DCM/THF = 3/1 (81.3 mL), followed by the addition of NaBH_4 (1.1906 g, 31.4724 mmol) and MeOH (25 mL) in small portions. After 24 h, the reaction was quenched by pouring into ice/dilute HCl mixture and layers were separated. The aqueous layer was extracted twice with DCM and the combined organic layers were washed with sat. NaHCO_3 , then with brine and dried over anhydrous Na_2SO_4 . The solvent was evaporated and the product was isolated after chromatographic purification (dry-flash chromatography, silica gel, gradient Hex/EA). Yield 1.4274 g (74%), pale yellow crystals, $\text{Mp} = 73\text{--}77\text{ }^\circ\text{C}$. IR (ATR): 3426m, 3320s, 2906s, 2854s, 1449m, 1397w, 1371w, 1347w, 1333w, 1302m, 1280w, 1233w, 1196w, 1158w, 1139m, 1105w, 1038s, 1016m, 972m, 945w, 911w, 813m, 790w, 735w, 675m, 657w, 602w, 482w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ) 3.26 (s, 2H, $-\text{CH}_2\text{OH}$), 2.37 – 2.25 (m, 4H, 2 $\times$ $-\text{CH}_2$), 2.22 – 2.17 (m, 2H, 2 $\times$ $-\text{CH}$), 2.15 (s, 2H, $-\text{CH}_2$), 1.75 – 1.61 (m, 2H, $-\text{CH}_2$), 1.58 – 1.49 (m, 4H, 2 $\times$ $-\text{CH}_2$). ^{13}C NMR (125 MHz, CDCl_3 , δ) 72.45, 65.92, 50.78, 48.90, 40.10, 37.30, 35.23, 32.22. EI-GC/MS m/z (%): 213.0 (2) $[\text{M} - \text{CH}_2\text{OH}]^+$, 165.1 (100) $[\text{M} - \text{Br}]^+$, 147.1 (29), 105.1 (36), 91.1 (26).

3-(((8-((7-Chloroquinolin-4-yl)amino)octyl)amino)methyl)adamantan-1-ol (6).

General procedure: A solution of **13** (200 mg, 1.0973 mmol) in dry DCM (15 mL), with added PCC (354.8 mg, 1.6459 mmol) was stirred at room temperature for 150 min. The crude product was purified by column chromatography (dry-flash, silica gel, gradient DCM/MeOH) affording 193.8 mg of **15** (98%), which was used in the next step without prior characterization.

Into the solution of **15** (197.8 mg, 1.0973 mmol) and **9** (335.6 mg, 1.0973 mmol) in DCM/MeOH = 1/2 (21 mL), AcOH (0.094 mL, 1.6436 mmol) was added in drops and the reaction mixture stirred overnight. Afterwards, NaBH_4 (249 mg, 6.5821 mmol) was carefully added and stirring continued for another 72 h. The solvent was removed under reduced pressure and the residue partitioned between DCM and NH_3 (aq, 2 M). The organic layer was washed with water, then brine, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The crude product was purified by column chromatography (dry-flash, silica gel, gradient DCM/MeOH). Yield 57.1 mg (11%), pale yellow oil. IR (ATR): 3313m, 2922s, 2850s, 1611m, 1581s, 1540m, 1453m, 1428m, 1368m, 1333m, 1312w, 1282w, 1204w, 1161w, 1137m, 1114w, 1080w, 1049w, 946w, 901w, 878w, 852w, 806w, 768w, 737w, 704w, 646w, 553w cm^{-1} . ^1H NMR (400 MHz, CDCl_3 , δ) 8.52 (d, $J = 5.3$ Hz, 1H, H-2), 7.95 (d, $J = 1.7$ Hz, 1H, H-8), 7.67 (d, $J = 8.9$ Hz, 1H, H-5), 7.34 (dd, $J_1 = 8.9$, $J_2 = 1.7$ Hz, 1H, H-6), 6.40 (d, $J = 5.4$ Hz, 1H, H-3), 5.06 (s,

1H, Ar-NH), 3.29 (q, $J = 6.8$ Hz, 2H, H-9), 2.57 (t, $J = 7.2$ Hz, 2H, H-16), 2.32 (s, 2H, H-17), 2.20 (s, 2H, $2 \times -CH(Ad)$), 1.80 – 1.62 (m, 6H, $2 \times -CH_2(Ad)$ and $-CH_2$ H-10), 1.58 – 1.52 (m, 2H, $-CH_2(Ad)$), 1.50 – 1.30 (m, 16H, $3 \times -CH_2(Ad)$ and $5 \times -CH_2$, H-11-15). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 152.15, 149.84, 149.25, 134.90, 128.94, 125.32, 121.01, 117.24, 99.18, 69.00, 61.97, 51.15, 48.63, 45.06, 43.39, 39.73, 37.41, 35.82, 30.72, 30.07, 29.55, 29.41, 29.00, 27.33, 27.20. ESI-HRMS (m/z): calc. for $[C_{28}H_{40}ClN_3O+H]^+$ 470.2933, found 470.2939.

*N*¹-((3-Bromoadamantan-1-yl)methyl)-*N*⁸-(7-chloroquinolin-4-yl)octane-1,8-diamine (7).

Following the above-described general procedure, **14** (150 mg, 0.6118 mmol) reacted with PCC (197.8 mg, 0.9176 mmol) in dry DCM (8.2 mL). The crude product was purified by column chromatography (dry-flash, silica gel, DCM) affording 139 mg of **16** (93%), which was used in the next step. Aldehyde **16** (139 mg, 0.5717 mmol) and amine **9** (209.8 mg, 0.6860 mmol) in DCM/MeOH = 1/2 (12 mL), were transformed into **7**, using AcOH (0.05 mL, 0.8743 mmol) and $NaBH_4$ (129.8 mg, 3.4311 mmol). The crude product was purified by column chromatography (dry-flash, silica gel, gradient prepared from DCM and mixture [MeOH/ $NH_3(aq)$ =9/1]). Yield 133.8 mg (44%), yellow oil. IR (ATR): 3267w, 3064w, 2928s, 2854m, 1611m, 1580s, 1540m, 1453m, 1368m, 1332m, 1304w, 1282w, 1250w, 1203w, 1138w, 1080w, 902w, 878w, 852w, 813w, 768w, 738w, 680w cm^{-1} . 1H NMR (400 MHz, $CDCl_3$, δ) 8.53 (d, $J = 5.4$ Hz, 1H, H-2), 7.95 (d, $J = 2.1$ Hz, 1H, H-8), 7.67 (d, $J = 9.0$ Hz, 1H, H-5), 7.35 (dd, $J_1 = 8.9$ Hz, $J_2 = 2.1$ Hz, 1H, H-6), 6.41 (d, $J = 5.4$ Hz, 1H, H-3), 5.04 (s, 1H, Ar-NH), 3.30 (q, $J = 7.1$ Hz, 2H, H-9), 2.57 (t, $J = 7.2$ Hz, 2H, H-16), 2.37 – 2.22 (m, 6H, H-17 and $2 \times -CH_2(Ad)$), 2.21 – 2.10 (m, 4H, $2 \times -CH(Ad)$ and $-CH_2(Ad)$), 1.80 – 1.30 (m, 18H, $3 \times -CH_2(Ad)$ and $6 \times -CH_2$, H-10-15). ^{13}C NMR (100 MHz, $CDCl_3$, δ) 152.10, 149.88, 149.18, 134.97, 128.91, 125.38, 120.99, 117.23, 99.20, 66.62, 61.66, 52.48, 51.11, 48.96, 43.42, 39.13, 39.08, 35.26, 32.50, 30.00, 29.56, 29.43, 29.02, 27.34, 27.22. ESI-HRMS (m/z): calc. for $[C_{28}H_{39}BrClN_3+H]^+$ 532.2089, found 532.2094.

*1-Adamantaneacetic acid (18).*⁸

1-Bromoadamantane **17** (5 g, 23.2407 mmol) was slowly added to 96% H_2SO_4 (20 mL) at 10 °C. Afterwards, 1,1-dichloroethene (17.6 mL, 221.1347 mmol) was added dropwise through the septum, over 1 h. Stirring was continued for another 3 h at the same temperature and another 3 h at 20 °C. The reaction mixture was poured into the ice/water mixture, transferred into a separatory funnel and extracted twice with diethyl ether. The combined organic layers were washed with aqueous NaOH (pH 9). Then, the separated aqueous layer was acidified to pH 3, during which a precipitate appeared, that was extracted twice with diethyl ether. Combined organic layers were washed with water, then brine and dried over anhydrous Na_2SO_4 . The product was isolated after the removal of the solvent under reduced pressure. Yield 4.0170 g (89%), white solid, Mp = 123-130 °C. IR (ATR): 2905s, 2848s, 2661m, 2191w, 2167w, 2106w, 1707s, 1645m, 1448m, 1404m, 1364w, 1346w, 1313m, 1269s, 1203w, 1145m, 1097w, 990w, 907m, 650w, 630w cm^{-1} . 1H NMR (500 MHz, $CDCl_3$, δ) 2.10 (s, 2H, $-CH_2COOH$), 2.02 – 1.95 (m, 3H, $3 \times -CH$), 1.74 – 1.61 (m, 12H, $6 \times -CH_2$). ^{13}C NMR (125 MHz, $CDCl_3$, δ) 178.57, 48.89, 42.43, 36.83, 32.84, 28.74.

*1-Adamantaneacetamide (19).*⁹

Into the ice-cold solution of **18** (1.5 g, 7.7212 mmol) in DCM (40 mL), in the presence of Et_3N (1.28 mL, 9.2341 mmol), $ClCOOEt$ (0.89 mL, 9.3076 mmol) was added slowly. After stirring at room temperature for 1 h 45 min, the mixture was evaporated to dryness and the residue was dissolved in DCM/THF = 3/1 (70.5 mL). Then, NH_3 (aq, 30%) (7.25 mL) was added dropwise and stirring of the mixture was continued for another 1 h. The solvents were

evaporated under reduced pressure, followed by the addition of water and EA. The aqueous layer was extracted once again with EA, and combined organic layers were washed with sat. NaHCO_3 , then with brine and dried over anhydrous Na_2SO_4 . The solvent was evaporated and the product was isolated after chromatographic purification (dry-flash, silica gel, gradient Hex /EA). Yield 1.13 g (76%), white solid, $\text{Mp} = 168\text{--}170\text{ }^\circ\text{C}$. IR (ATR): 3372s, 3190m, 2902s, 2849s, 2678w, 1665s, 1626s, 1447m, 1402m, 1363m, 1344w, 1313w, 1246w, 1207w, 1167w, 1130w, 1101w, 987w, 947w, 887w, 805w, 749w, 674w, 601w, 461w, 418w cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ) 5.72 – 5.27 (m, 2H, $-\text{NH}_2$), 2.02 – 1.95 (m, 5H, $2\times -\text{CH}$ and $-\text{CH}_2\text{CONH}_2$), 1.75 – 1.62 (m, 12H, 6 $-\text{CH}_2$). ^{13}C NMR (125 MHz, CDCl_3 , δ) 173.64, 51.24, 42.70, 36.86, 32.69, 28.76. EI-GC/MS m/z (%): 193.1 (30) $[\text{M}]^+$, 135.1 (100) $[\text{M} - \text{CH}_2\text{CONH}_2]^+$, 93.1 (17), 79.1 (16).

3-Bromo-(1-adamantaneacetamide) (20).

A suspension of *t*-BuOH (7.5 mL, 78.9261 mmol) and LiBr (10.28 g, 118.3650 mmol) was cooled in an ice bath and 48% HBr (17.8 mL) was added in drops during 30 min. After stirring the mixture at room temperature for 3 h, the top organic layer was separated, washed with water and dried over anhydrous Na_2SO_4 . The product was isolated after solvent removal under reduced pressure to give 7.3142 g of *t*-BuBr (68%), which was used in the next step without prior characterization.

Into the mixture of CCl_4 (14.8 mL) and 96% H_2SO_4 (19.7 mL) at $10\text{ }^\circ\text{C}$, **19** (1.11 g, 5.7427 mmol) and *t*-BuBr (3.93 g, 28.6819 mmol) were added. After stirring at room temperature for 2 h, the reaction mixture was poured onto ice and diluted with DCM. The separated aqueous layer was extracted once again with DCM, combined organic layers were washed with water, then brine and dried over anhydrous Na_2SO_4 . The solvent was evaporated and the product was isolated after chromatographic purification (dry-flash, silica gel, gradient Hex /EA). Yield 1.2414 g (80%), brownish crystals, $\text{Mp} = 104\text{--}110\text{ }^\circ\text{C}$. IR (ATR): 3486m, 3369m, 3167s, 2909s, 2853m, 1675s, 1448m, 1395m, 1336m, 1298m, 1278m, 1186m, 1102m, 1010w, 976m, 933m, 894w, 813m, 711m, 674m, 604m, 524w, 482m cm^{-1} . ^1H NMR (500 MHz, CDCl_3 , δ) 5.58 (d, $J = 153.4\text{ Hz}$, 2H, $-\text{NH}_2$), 2.36 – 2.23 (m, 6H, $3\times -\text{CH}_2$), 2.21 – 2.15 (m, 2H, $2\times -\text{CH}$), 2.03 (s, 2H, $-\text{CH}_2\text{CONH}_2$), 1.72 – 1.61 (m, 6H, $3\times -\text{CH}_2$). ^{13}C NMR (125 MHz, CDCl_3 , δ) 172.73, 65.38, 53.86, 49.68, 48.47, 40.55, 37.42, 34.76, 32.47. EI-GC/MS m/z (%): 192.1 (100) $[\text{M} - \text{Br}]^+$, 133.1 (23), 91.0 (23).

3-(2-amino-2-oxoethyl)adamantane-1-carboxylic acid (21).

Into the 96% H_2SO_4 (22.2 mL), cooled to $0\text{ }^\circ\text{C}$, **20** (1.2 g, 4.4088 mmol) was added, followed by Hex (3.12 mL) and HCOOH (2.7 mL). The mixture was spontaneously warmed to room temperature and stirred for 22 h. The reaction was quenched by carefully pouring onto ice and the pH was adjusted to 3 using aqueous NaOH, during which a precipitate appeared. The product was isolated after filtration and dried under reduced pressure. Yield 1.04 g (99%), white solid, $\text{Mp} = 224\text{--}228\text{ }^\circ\text{C}$. IR (ATR): 3423s, 3340m, 3203m, 2926s, 2851m, 2513w, 2168w, 1940w, 1682s, 1645s, 1577m, 1450m, 1410m, 1361w, 1327m, 1276s, 1164m, 1026w, 999w, 744w, 703w, 672w, 633w, 610w, 516w, 469w, 420w cm^{-1} . ^1H NMR (500 MHz, CD_3OD , δ) 2.14 – 2.09 (m, 2H, $2\times -\text{CH}$), 2.04 (s, 2H, $-\text{CH}_2\text{CONH}_2$), 1.92 – 1.79 (m, 6H, $3\times -\text{CH}_2$), 1.74 – 1.62 (m, 6H, $3\times -\text{CH}_2$). ^{13}C NMR (125 MHz, CD_3OD , δ) 181.26, 176.51, 50.70, 44.86, 42.62, 42.47, 39.40, 36.77, 33.79, 29.93. UPLC-MS m/z (%): 473.71 (100) $[2\text{M} - \text{H}]^-$, 236.41 (50) $[\text{M} - \text{H}]^-$.

2-(3-(Hydroxymethyl)adamantan-1-yl)acetamide (22).

A solution of **21** (1.025 g, 4.3194 mmol) in DCM (23.5 mL), with Et₃N (0.72 mL, 5.1942 mmol) was cooled in an ice bath and ClCOOEt (0.5 mL, 5.2290 mmol) was added in drops. After stirring at room temperature for 90 min, the mixture was evaporated to dryness and the residue was dissolved in DCM/THF = 3/1 (42.1 mL), followed by the addition of NaBH₄ (653.6 mg, 17.2773 mmol) and MeOH (12.7 mL) in small portions. After 20 h, the reaction was quenched by pouring into ice/dilute HCl mixture and layers were separated. The aqueous layer was neutralized to pH 7, using aqueous NaHCO₃, extracted three times with EA and the combined organic layers were washed with brine. The product was isolated after the solvent was evaporated under reduced pressure. Yield 434.1 mg (45%), white crystals, Mp = 161-163 °C. IR (ATR): 3749w, 3305s, 3181s, 2904s, 2847s, 1666s, 1626s, 1541w, 1513w, 1453m, 1404m, 1363m, 1339m, 1315w, 1199w, 1165m, 1063m, 1036m, 608m cm⁻¹. ¹H NMR (400 MHz, CD₃OD, δ) 3.13 (s, 2H, -CH₂OH), 2.09 – 2.01 (m, 2H, 2× -CH), 1.98 (s, 2H, -CH₂CONH₂), 1.70 – 1.33 (m, 12H, 6× -CH₂). ¹³C NMR (125 MHz, CD₃OD, δ) 176.82, 73.60, 51.02, 45.30, 43.29, 39.53, 37.45, 36.54, 33.95, 30.18. EI-GC/MS *m/z* (%): 223.1 (10) [M]⁺, 192.1 (100) [M - CH₂OH]⁺, 133.1 (27), 91.1 (28).

2-(3-(((8-((7-Chloroquinolin-4-yl)amino)octyl)amino)methyl)adamantan-1-yl)acetamide (8).

Following the above-described general procedure, **22** (434.1 mg, 1.9438 mmol) reacted with PCC (628.6 mg, 2.9161 mmol) in dry DCM (27.7 mL). The crude product was purified by column chromatography (dry-flash, silica gel, gradient DCM/MeOH) affording 140.6 mg of **23** (33%), which was used in the next step. Aldehyde **23** (140.6 mg, 0.6353 mmol) and amine **9** (233 mg, 0.7624 mmol) in DCM/MeOH = 1/2 (15 mL), were transformed into **8**, using AcOH (0.073 mL, 1.2764 mmol) and NaBH₄ (144.2 mg, 3.8118 mmol). The crude product was purified by column chromatography (dry-flash chromatography, silica gel, gradient DCM/MeOH, then multiple preparative thin-layer chromatography, silica gel, developed 2 times with MeOH). Yield 46 mg (14%), yellowish oil. IR (ATR): 3337m, 2927s, 2852m, 1667m, 1612m, 1580s, 1541w, 1452m, 1369w, 1333w, 1282w, 1138w, 1081w, 904w, 879w, 853w, 808w, 738w, 647w cm⁻¹. ¹H NMR (500 MHz, CDCl₃, δ) 8.53 (d, *J* = 5.4 Hz, 1H, H-2), 7.95 (d, *J* = 2.2 Hz, 1H, H-8), 7.70 (d, *J* = 8.9 Hz, 1H, H-5), 7.36 (dd, *J*₁ = 8.8 Hz, *J*₂ = 2.2 Hz, 1H, H-6), 6.41 (d, *J* = 5.4 Hz, 1H, H-3), 5.62 (bs, 2H, -NH₂), 5.15 – 5.06 (m, 1H, Ar-NH), 3.30 (q, *J* = 7.1 Hz, 2H, H-9), 2.58 (t, *J* = 7.4 Hz, 2H, H-16), 2.30 (s, 2H, H-17), 2.09 – 2.03 (m, 2H, 2× -CH(Ad)), 2.00 (s, 2H, -CH₂CONH₂), 1.75 (quint, *J* = 7.3 Hz, 2H, H-10), 1.63 – 1.41 (m, 16H, 6× -CH₂(Ad) and 2× -CH₂, H-11 and H-15), 1.41 – 1.29 (m, 6H, 3× -CH₂, H-(12-14)). ¹³C NMR (125 MHz, CDCl₃, δ) 173.48, 152.20, 149.89, 149.28, 134.93, 128.94, 125.35, 121.10, 117.27, 99.19, 62.39, 51.06, 50.82, 45.69, 43.38, 42.23, 40.20, 36.36, 34.26, 33.26, 29.52, 29.47, 29.34, 28.95, 28.85, 27.28, 27.16. ESI-HRMS (*m/z*): calc. for [C₃₀H₄₃ClN₄O+H]⁺ 511.3198, found 511.3197.

2. LIST OF INTERACTIONS BETWEEN THE TESTED COMPOUNDS AND AChE

2.1. *Binding site of AChE*

The first is the catalytic anionic site (CAS) of the AChE, which is at the bottom of the gorge and composed of a catalytic triad, oxyanion hole, and a choline-binding site. A peripheral anionic site (PAS) is located at the entrance and consists of Tyr72, Tyr124, Asp74, Tyr341, and Trp286.¹⁰

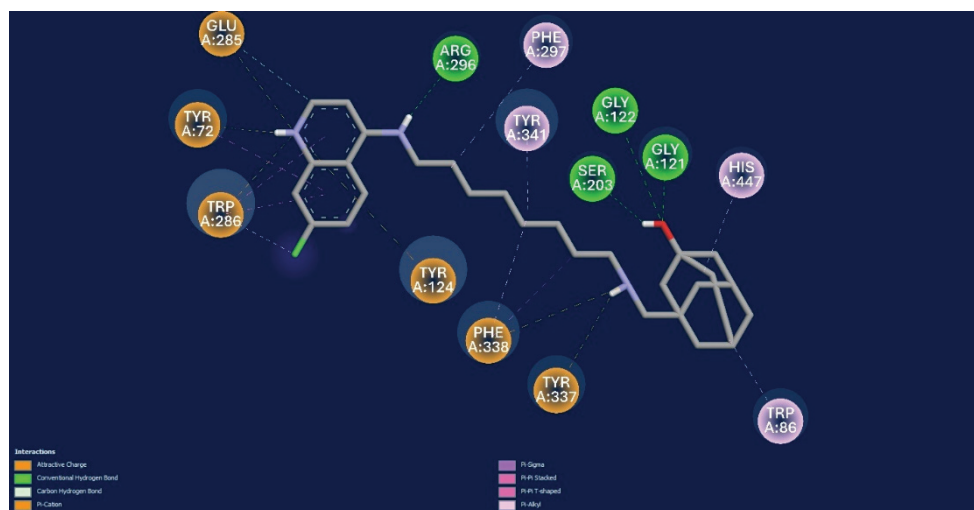
The binding site for docking was determined as the centre of the following residues: Tyr72, Trp86, Tyr124, Tyr133, Ser203, Trp236, Trp286, Phe297, Phe297, Glu334, Tyr337, Phe338, Tyr341, His447, and Tyr449.

Abbreviations for types of interaction

ES – electrostatic; H-Bond – hydrogen bond; Hpho – hydrophobic; Attractive Ch – attractive charge; H₂O H-Bond – water hydrogen bond; Conv. H-Bond – conventional hydrogen bond; π – π -orbitals; HD – H-Donor; HA – H-Acceptor; + – positive; – – negative

TABLE S-I. Scores for docked ligands.

Comp.	6	7	8
IFDScore (kJ mol ⁻¹)	-923.44	-919.54	-919.05

Fig. S1. Map of interactions of compound **6** with AChE.TABLE S-II. Ligand interactions of **6** with AChE.

TYPE	Category	Type	FROM	TO
6:N3 - GLU285:OE1	ES	Attractive Charge	6:N3, +	GLU285:OE1, -
GLY121:HN - 6:O1	H-Bond	Conv. H-Bond	GLY121:HN, HD	6:O1, HA
GLY122:HN - 6:O1	H-Bond	Conv. H-Bond	GLY122:HN, HD	6:O1, HA
6:H3 - ARG296:O	H-Bond	Conv. H-Bond	6:H3, HD	ARG296:O, HA
6:H35 - SER203:OG	H-Bond	Conv. H-Bond	6:H35, HD	SER203:OG, HA
6:C26 - GLU285:OE1	H-Bond	Carbon H-Bond	6:C26, HD	GLU285:OE1, HA
6:N2 - PHE338	ES	π -Cation	6:N2, +	PHE338, π
6:N3 - TYR124	ES	π -Cation	6:N3, +	TYR124, π
6:N3 - TRP286	ES	π -Cation	6:N3, +	TRP286, π
6:N3 - TRP286	ES	π -Cation	6:N3, +	TRP286, π
6:H20 - TYR337	H-Bond; ES	π -Cation; π -Donor H-Bond	6:H20, +;HD	TYR337, π ; π
6:H42 - TYR72	H-Bond; ES	π -Cation; π -Donor H-Bond	6:H42, +;HD	TYR72, π ; π
6:C12 - PHE338	Hpho.	π -Sigma	6:C12, C-H	PHE338, π
TRP286 - 6	Hpho.	π - π Stacked	TRP286, π	6, π
TRP286 - 6	Hpho.	π - π Stacked	TRP286, π	6, π
TRP286 - 6	Hpho.	π - π Stacked	TRP286, π	6, π
TRP286 - 6	Hpho.	π - π Stacked	TRP286, π	6, π
TYR72 - 6	Hpho.	π - π T-shaped	TYR72, π	6, π
TRP86 - 6	Hpho.	π -Alkyl	TRP86, π	6, Alkyl
TRP86 - 6	Hpho.	π -Alkyl	TRP86, π	6, Alkyl
TRP286 - 6:CL1	Hpho.	π -Alkyl	TRP286, π	6:CL1, Alkyl
TRP286 - 6:CL1	Hpho.	π -Alkyl	TRP286, π	6:CL1, Alkyl
PHE297 - 6	Hpho.	π -Alkyl	PHE297, π	6, Alkyl
PHE338 - 6	Hpho.	π -Alkyl	PHE338, π	6, Alkyl
TYR341 - 6	Hpho.	π -Alkyl	TYR341, π	6, Alkyl
HIS447 - 6	Hpho.	π -Alkyl	HIS447, π	6, Alkyl

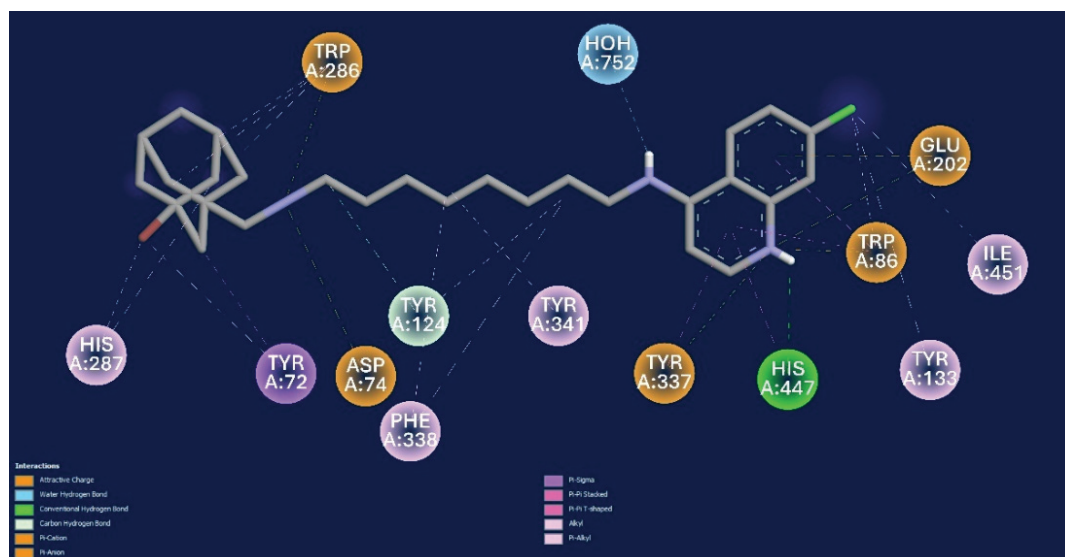
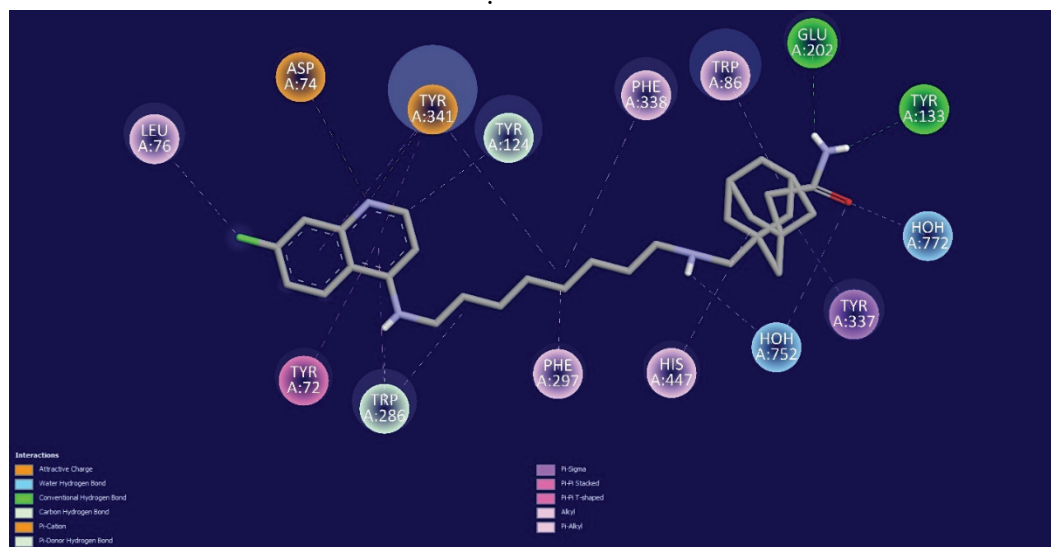


Fig. S2. Map of interactions of compound 7 with AChE.

TABLE S-III. Interactions of compound **7** with AChE.

TYPE	Category	Type	FROM	TO
7:N2 - ASP74:OD2	ES	Attractive Ch.	7:N2, +	ASP74:OD2, –
7:N3 - GLU202:OE2	ES	Attractive Ch.	7:N3, +	GLU202:OE2, –
7:H3 - HOH752:OH2	H-Bond	H ₂ O H-Bond; Conv. H-Bond	7:H3, HD	HOH752:OH2, HA
7:H41 - HIS447:O	H-Bond	Conv. H-Bond	7:H41, HD	HIS447:O, HA
7:C13 - TYR124:OH	H-Bond	Carbon H-Bond	7:C13, HD	TYR124:OH, HA
7:N2 - TRP286	ES	π -Cation	7:N2, +	TRP286, π
7:N2 - TRP286	ES	π -Cation	7:N2, +	TRP286, π
7:N3 - TRP86	ES	π -Cation	7:N3, +	TRP86, π
7:N3 - TRP86	ES	π -Cation	7:N3, +	TRP86, π
7:N3 - TYR337	ES	π -Cation	7:N3, +	TYR337, π
GLU202:OE1 - 7	ES	π -Anion	GLU202:OE1, -	7, π
7:C24 - TYR72	Hpho	π -Sigma	7:C24, C-H	TYR72, π
TRP86 - 7	Hpho	π - π Stacked	TRP86, π	7, π
TRP86 - 7	Hpho	π - π Stacked	TRP86, π	7, π
TRP86 - 7	Hpho	π - π Stacked	TRP86, π	7, π
TRP86 - 7	Hpho	π - π Stacked	TRP86, π	7, π
TYR337 - 7	Hpho	π - π T-shaped	TYR337, π	7, π
HIS447 - 7	Hpho	π - π T-shaped	HIS447, π	7, π
7:CL1 - ILE451	Hpho	Alkyl	7:CL1, Alkyl	ILE451, Alkyl
TYR72 - 7:BR1	Hpho	π -Alkyl	TYR72, π	7:BR1, Alkyl
TRP86 - 7:CL1	Hpho	π -Alkyl	TRP86, π	7:CL1, Alkyl
TYR124 - 7	Hpho	π -Alkyl	TYR124, π	7, Alkyl
TYR133 - 7:CL1	Hpho	π -Alkyl	TYR133, π	7:CL1, Alkyl
TRP286 - 7	Hpho	π -Alkyl	TRP286, π	7, Alkyl
TRP286 - 7	Hpho	π -Alkyl	TRP286, π	7, Alkyl
TRP286 - 7:C23	Hpho	π -Alkyl	TRP286, π	7:C23, Alkyl
TRP286 - 7	Hpho	π -Alkyl	TRP286, π	7, Alkyl
HIS287 - 7:C23	Hpho	π -Alkyl	HIS287, π	7:C23, Alkyl
HIS287 - 7:BR1	Hpho	π -Alkyl	HIS287, π	7:BR1, Alkyl
PHE338 - 7	Hpho	π -Alkyl	PHE338, π	7, Alkyl
PHE338 - 7	Hpho	π -Alkyl	PHE338, π	7, Alkyl
TYR341 - 7	Hpho	π -Alkyl	TYR341, π	7, Alkyl

Fig. S3. Map of interactions of compound **8** with AChE.TABLE S-IV. Ligand interactions of **8** with AChE.

TYPE	Category	Type	FROM	TO
8:N4 - ASP74:OD1	ES	Attractive Charge	8:N4, +	ASP74:OD1, -
HOH752:H1 - 8:O1	H-Bond	H ₂ O H-Bond; Conv. H-Bond	HOH752:H1, HD	8:O1, HA
HOH772:H1 - 8:O1	H-Bond	H ₂ O H-Bond; Conv. H-Bond	HOH772:H1, HD	8:O1, HA
8:H20 - HOH752:OH2	H-Bond	H ₂ O H-Bond; Conv. H-Bond	8:H20, HD	HOH752:OH2, HA
8:H37 - GLU202:OE1	H-Bond	Conv. H-Bond	8:H37, HD	GLU202:OE1, HA
8:H38 - TYR133:OH	H-Bond	Conv. H-Bond	8:H38, HD	TYR133:OH, HA
8:C28 - TYR124:OH	H-Bond	Carbon H-Bond	8:C28, HD	TYR124:OH, HA
8:N4 - TYR341	ES	π -Cation	8:N4, +	TYR341, π -Orbitals
8:H3 - TRP286	H-Bond	π -Donor H-Bond	8:H3, HD	TRP286, π -Orbitals
8:C20 - TYR337	Hpho.	π -Sigma	8:C20, C-H	TYR337, π -Orbitals
TYR341 - 8	Hpho.	π - π Stacked	TYR341, π -Orbitals	8, π -Orbitals
TYR341 - 8	Hpho.	π - π Stacked	TYR341, π -Orbitals	8, π -Orbitals
TYR72 - 8	Hpho.	π - π T-shaped	TYR72, π -Orbitals	8, π -Orbitals
TRP286 - 8	Hpho.	π - π T-shaped	TRP286, π -Orbitals	8, π -Orbitals
TRP286 - 8	Hpho.	π - π T-shaped	TRP286, π -Orbitals	8, π -Orbitals
8:CL1 - LEU76	Hpho.	Alkyl	8:CL1, Alkyl	LEU76, Alkyl
TRP86 - 8	Hpho.	π -Alkyl	TRP86, π -Orbitals	8, Alkyl
TRP86 - 8	Hpho.	π -Alkyl	TRP86, π -Orbitals	8, Alkyl
TRP286 - 8	Hpho.	π -Alkyl	TRP286, π -Orbitals	8, Alkyl
PHE297 - 8	Hpho.	π -Alkyl	PHE297, π -Orbitals	8, Alkyl
PHE338 - 8	Hpho.	π -Alkyl	PHE338, π -Orbitals	8, Alkyl
TYR341 - 8	Hpho.	π -Alkyl	TYR341, π -Orbitals	8, Alkyl
HIS447 - 8	Hpho.	π -Alkyl	HIS447, π -Orbitals	8, Alkyl

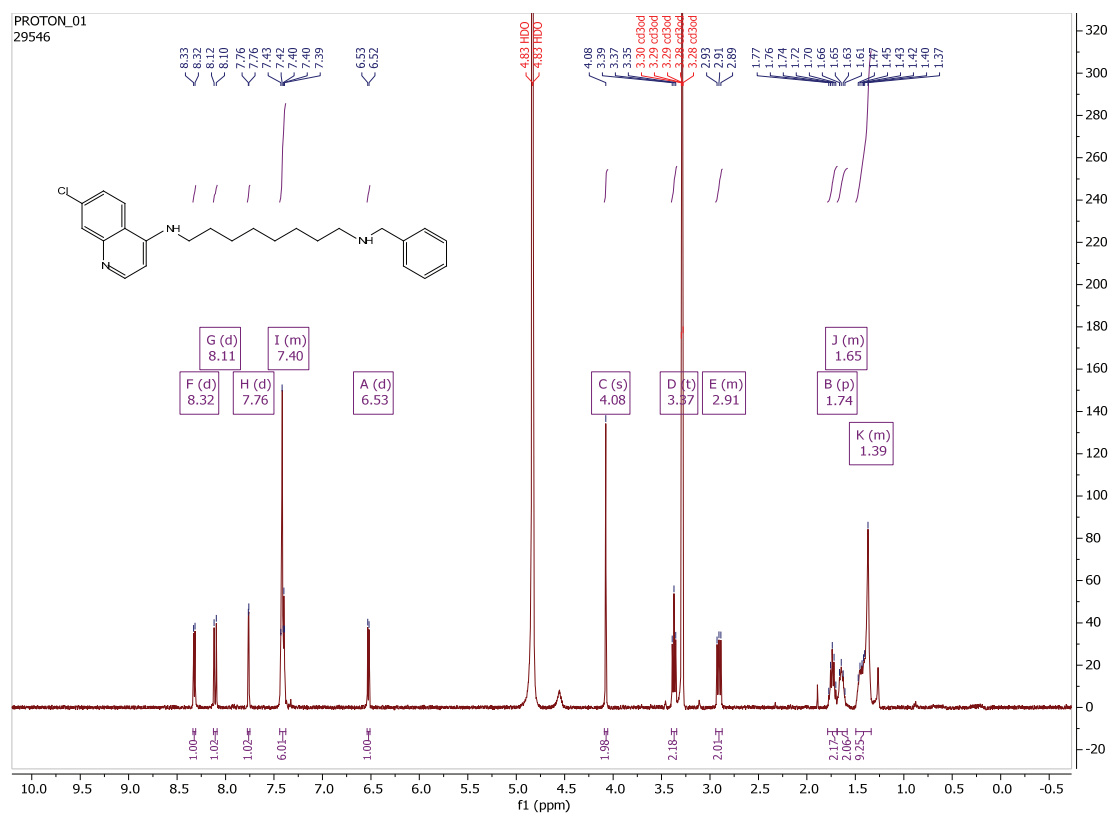
4. *IN SILICO* CALCULATIONS

TABLE S-V. In silico physicochemical properties of 4-AQ hybrids with adamantane.

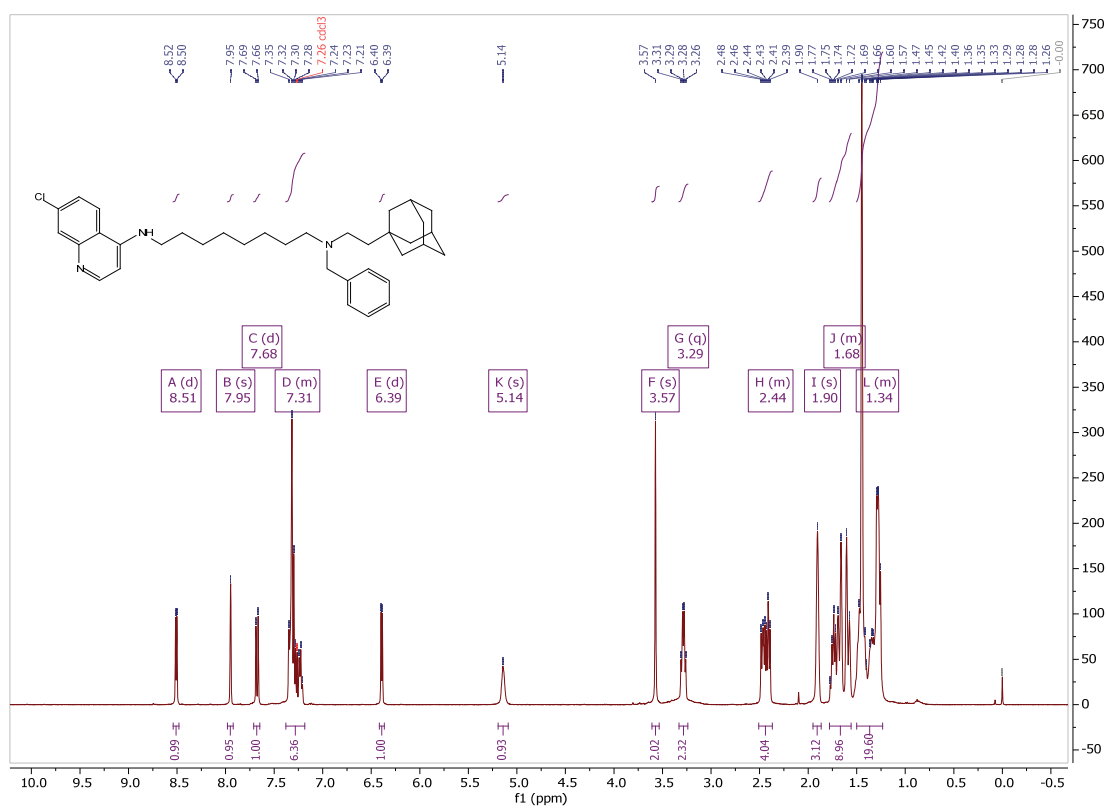
Comp.	MW (g/mol)	RB	HBA	HBD	TPSA (Å ²)	log <i>P</i>	p <i>K</i> _{a1} ^a	p <i>K</i> _{a2} ^a	log <i>D</i> ^b	CNS MPO ^c
1	454.09	12	3	2	36.95	6.625	7.71	11.46	3.00	2.2
2	395.98	12	3	2	36.95	5.923	7.70	9.65	3.28	2.6
3	468.12	13	3	2	36.95	6.913	7.71	11.38	3.30	1.9
4	544.21	14	3	1	28.16	8.732	7.71	10.24	5.54	1.2
5	558.24	15	3	1	28.16	9.021	7.70	9.65	6.36	1.4
6	470.09	12	4	3	57.18	5.31	7.71	11.15	1.74	2.4
7	532.99	12	3	2	36.95	6.85	7.71	11.45	3.23	1.7
8	511.14	14	4	3	80.04	5.242	7.71	11.45	1.62	2.2
Tacrine	198.26	0	2	1	38.91	2.628	9.35	-	1.05	5.1

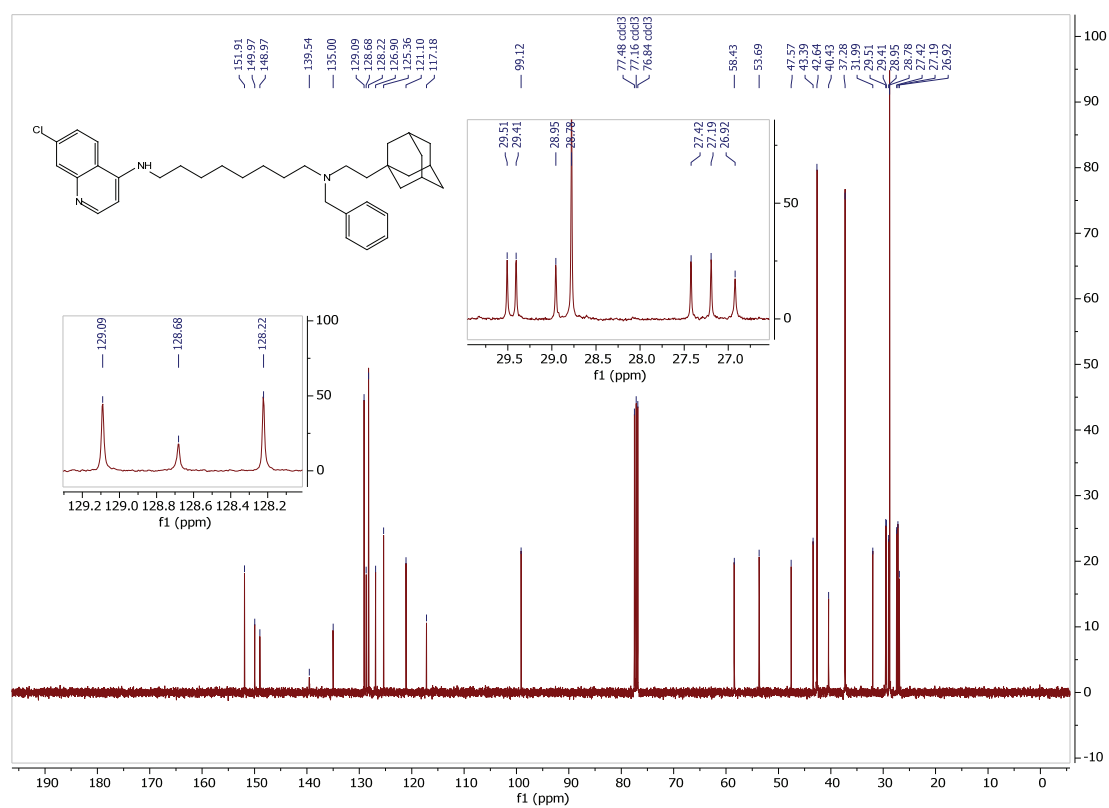
^a p*K*_{a1} belongs to the quinoline ring, p*K*_{a2} belongs to the terminal basic amino group; ^b log *D* value at pH = 7.4; ^c CNS

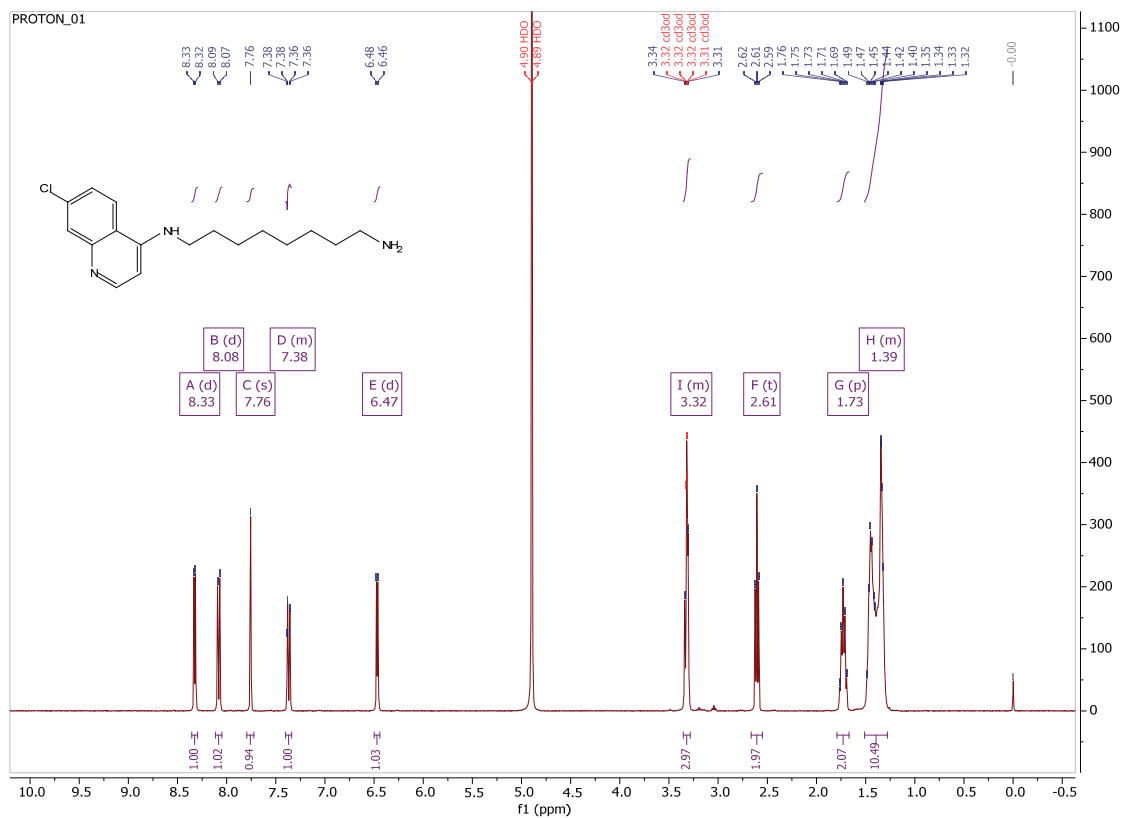
MPO data were generated following instruction published in reference T. T. Wager, X. Hou, P. R. Verhoest, A. Villalobos, *ACS Chem. Neurosci.*, **1** (2010) 435. <https://doi.org/10.1021/cn100008c>;

4. ^1H AND ^{13}C NMR SPECTRA ^1H NMR spectrum of N^1 -benzyl- N^8 -(7-chloroquinolin-4-yl)octane-1,8-diamine (2)

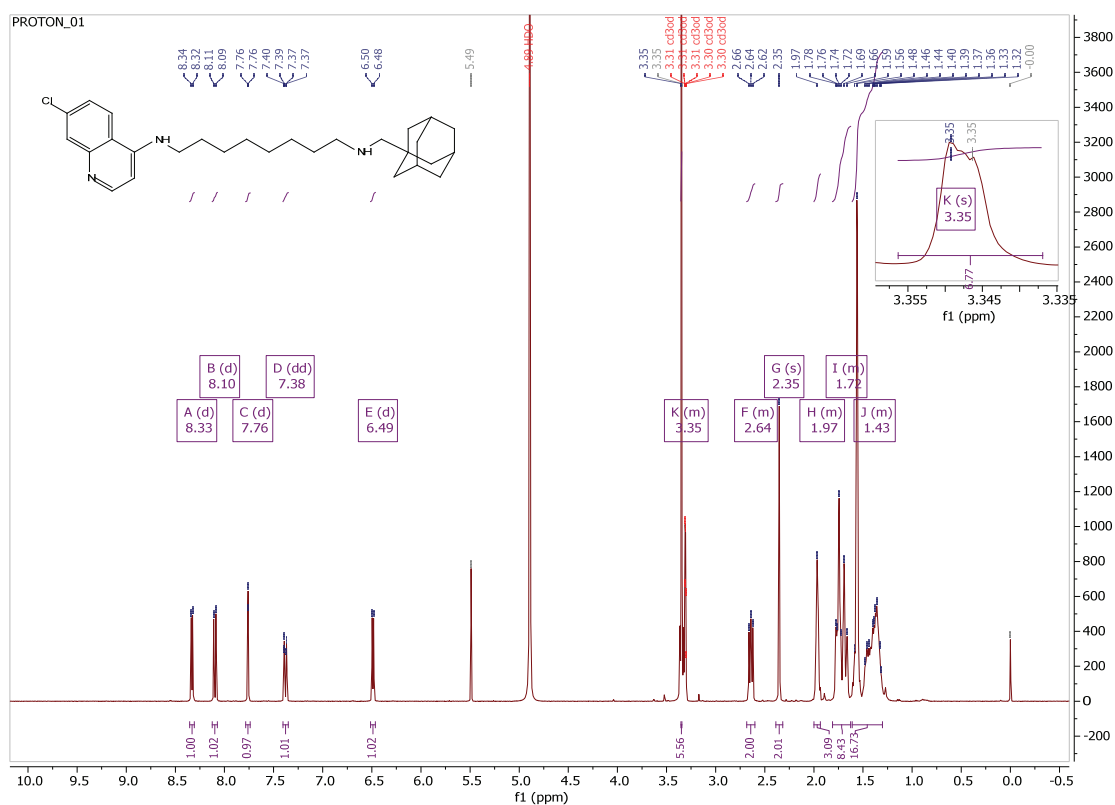
^1H NMR spectrum of N^1 -(2-adamantan-1-yl)ethyl)- N^1 -benzyl- N^8 -(7-chloroquinolin-4-yl)octane-1,8-diamine (5)



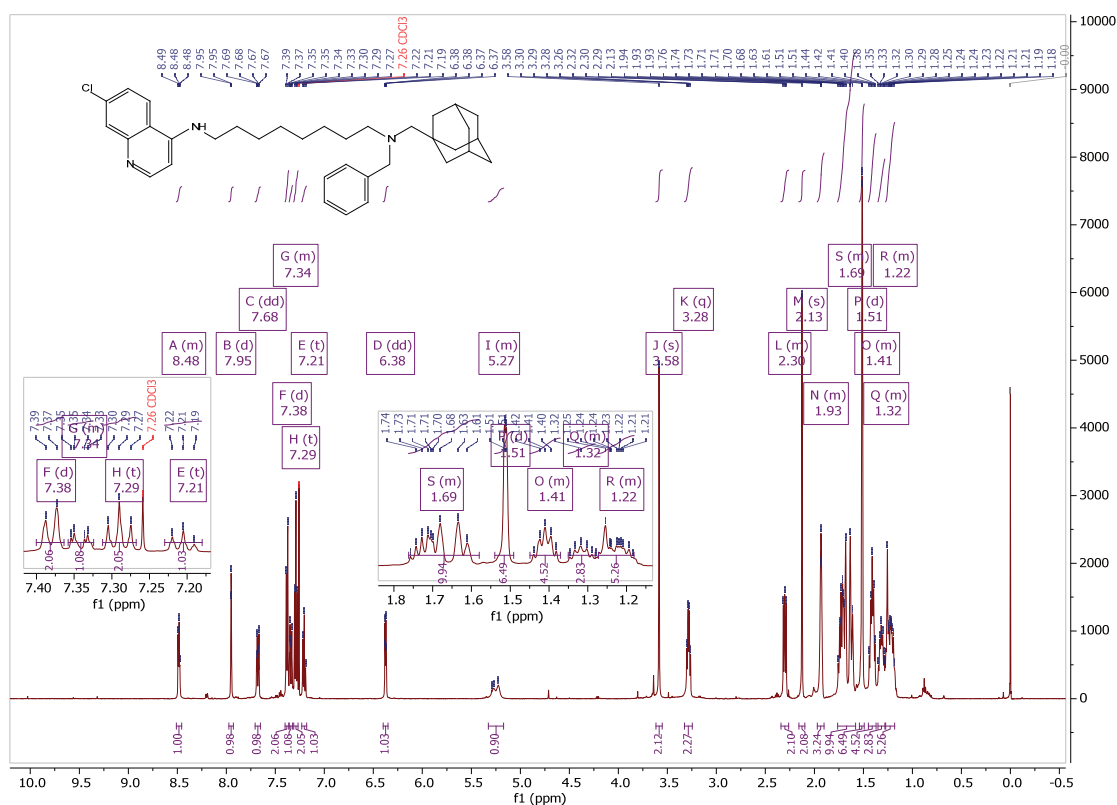
¹³C NMR spectrum of *N*¹-(2-(adamantan-1-yl)ethyl)-*N*¹-benzyl-*N*⁸-(7-chloroquinolin-4-yl)octane-1,8-diamine (5)

¹H NMR spectrum of *N*¹-(7-chloroquinolin-4-yl)octane-1,8-diamine (9)

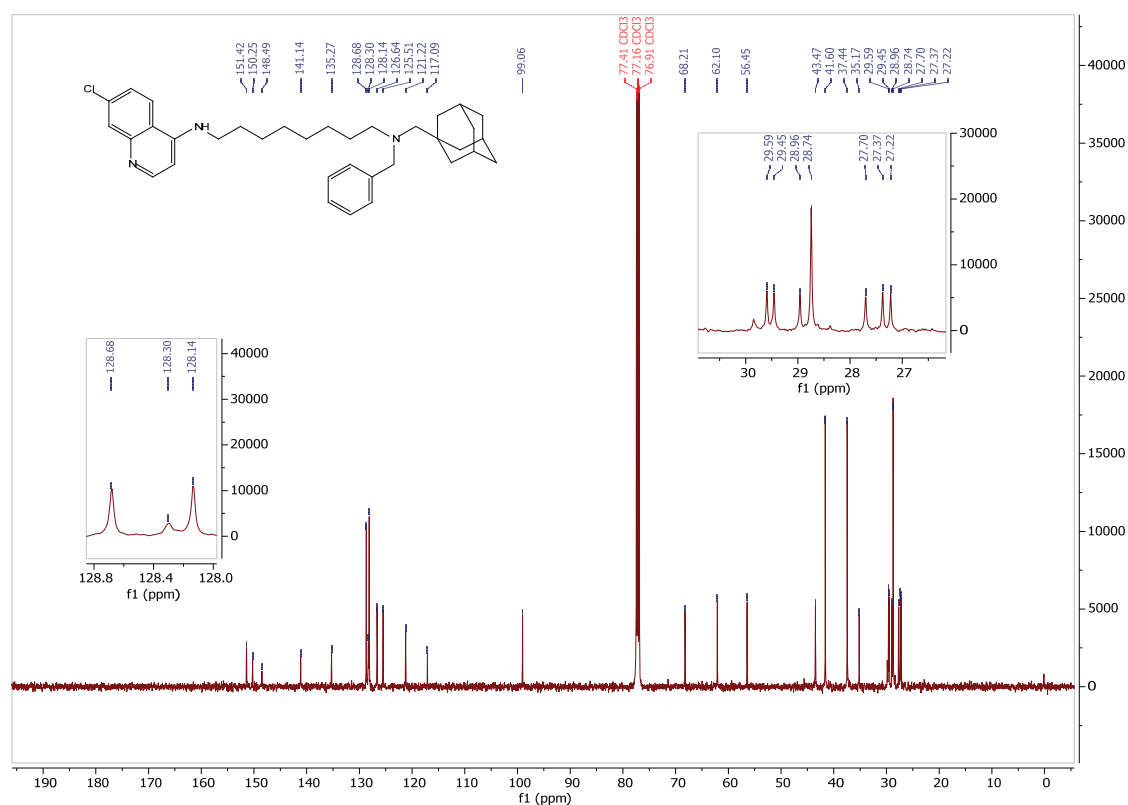
¹H NMR spectrum of *N*¹-((adamantan-1-yl)methyl)-*N*⁸-(7-chloroquinolin-4-yl)octane-1,8-diamine (1)



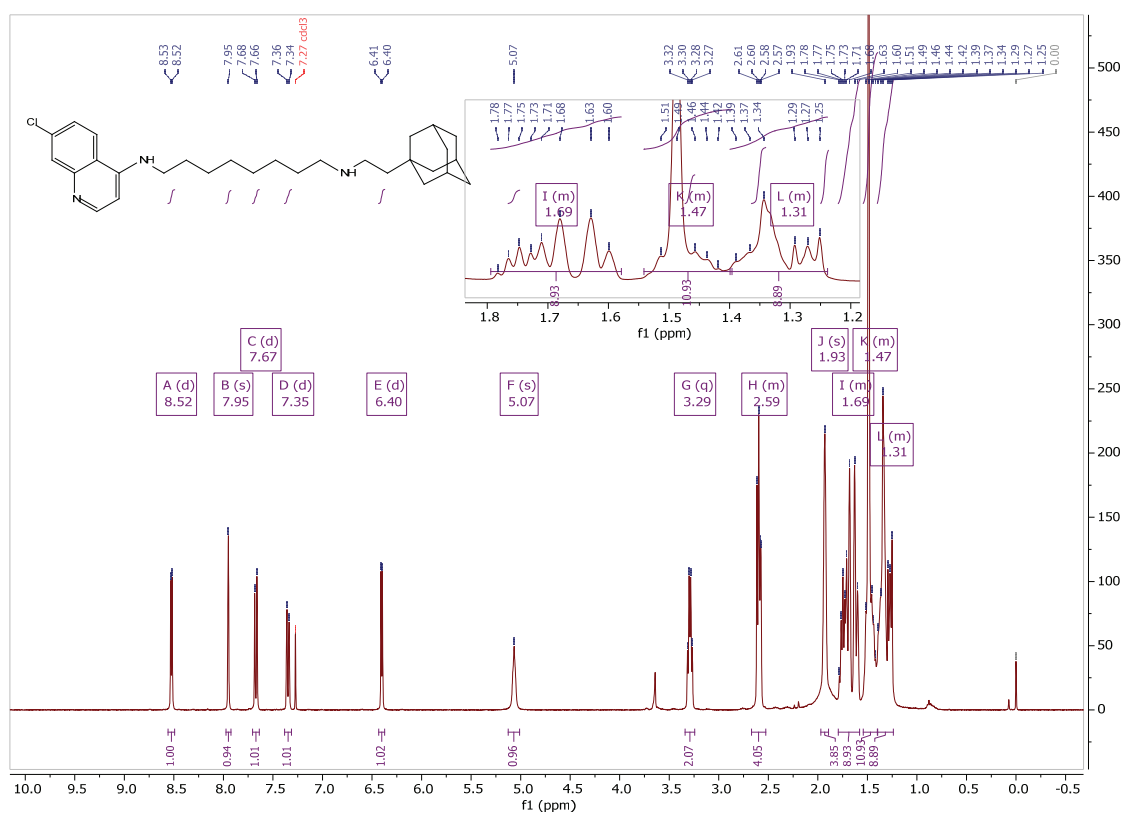
^1H NMR spectrum of N^1 -((adamantan-1-yl)methyl)- N^1 -benzyl- N^8 -(7-chloroquinolin-4-yl)octane-1,8-diamine (4)



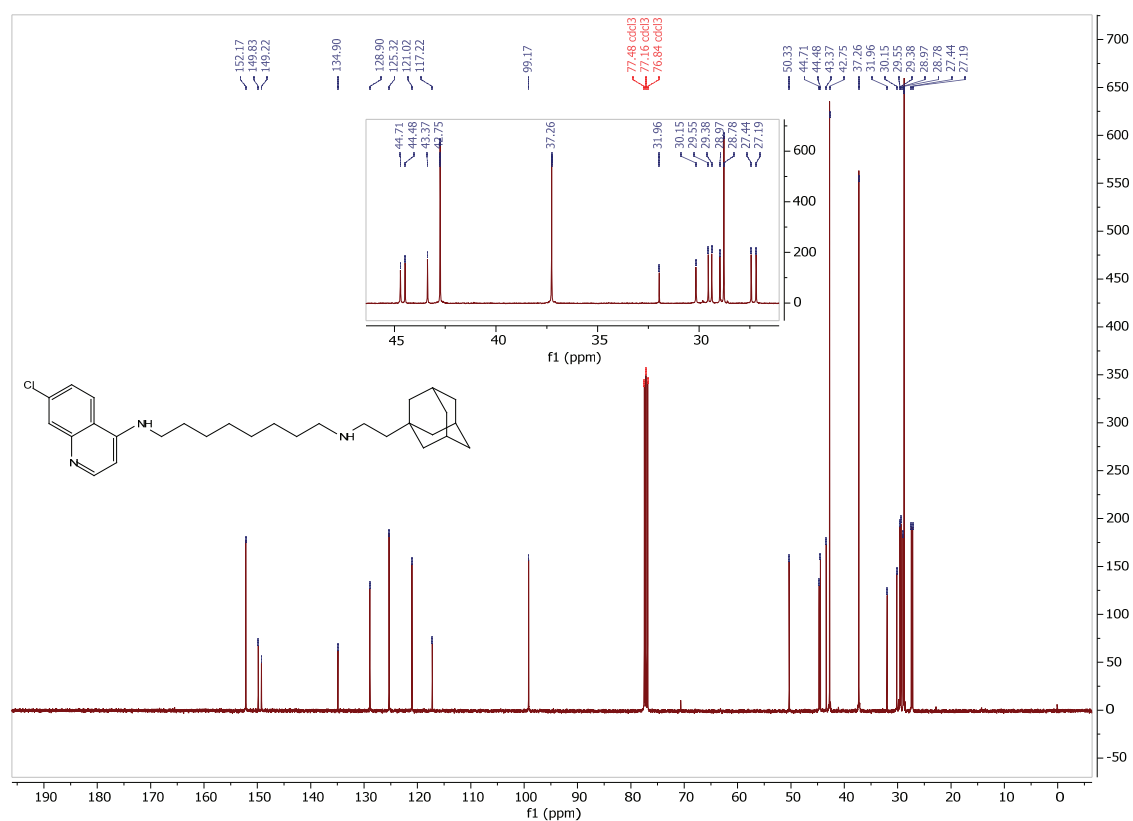
^{13}C NMR spectrum of N^1 -((adamantan-1-yl)methyl)- N^1 -benzyl- N^8 -(7-chloroquinolin-4-yl)octane-1,8-diamine (4)

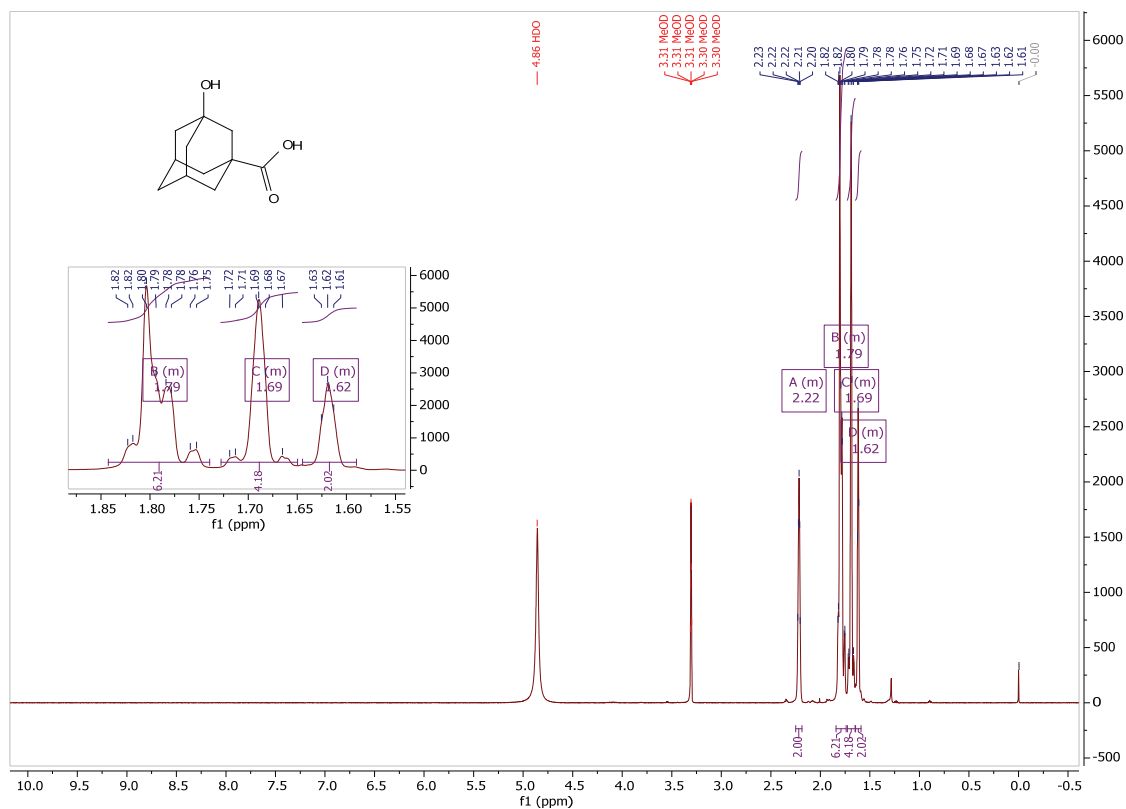


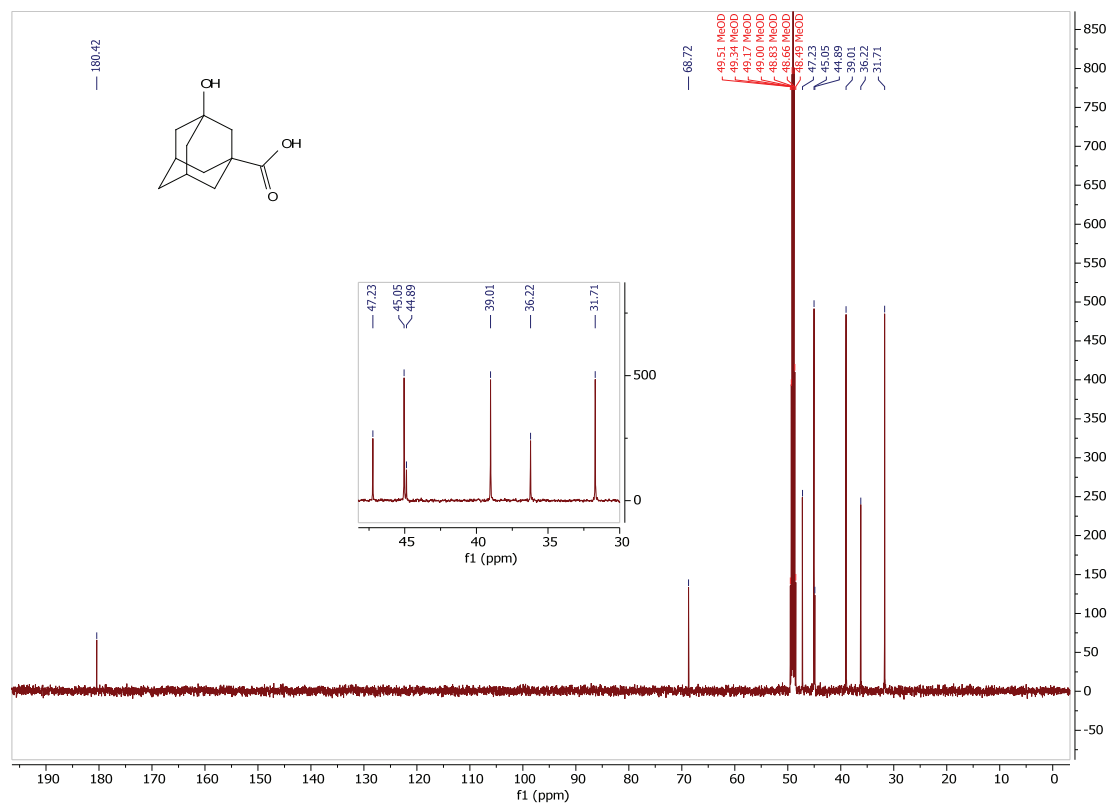
^1H NMR spectrum of N^1 -(2-(adamantan-1-yl)ethyl)- N^8 -(7-chloroquinolin-4-yl)octane-1,8-diamine (3)

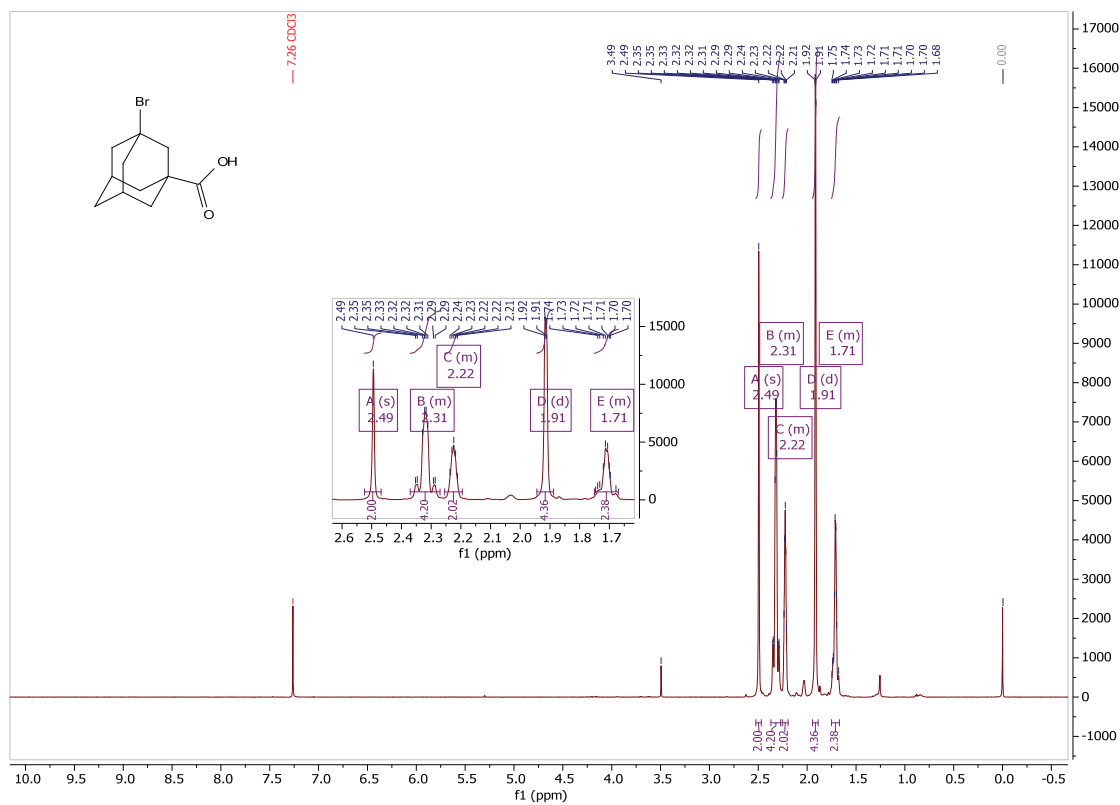


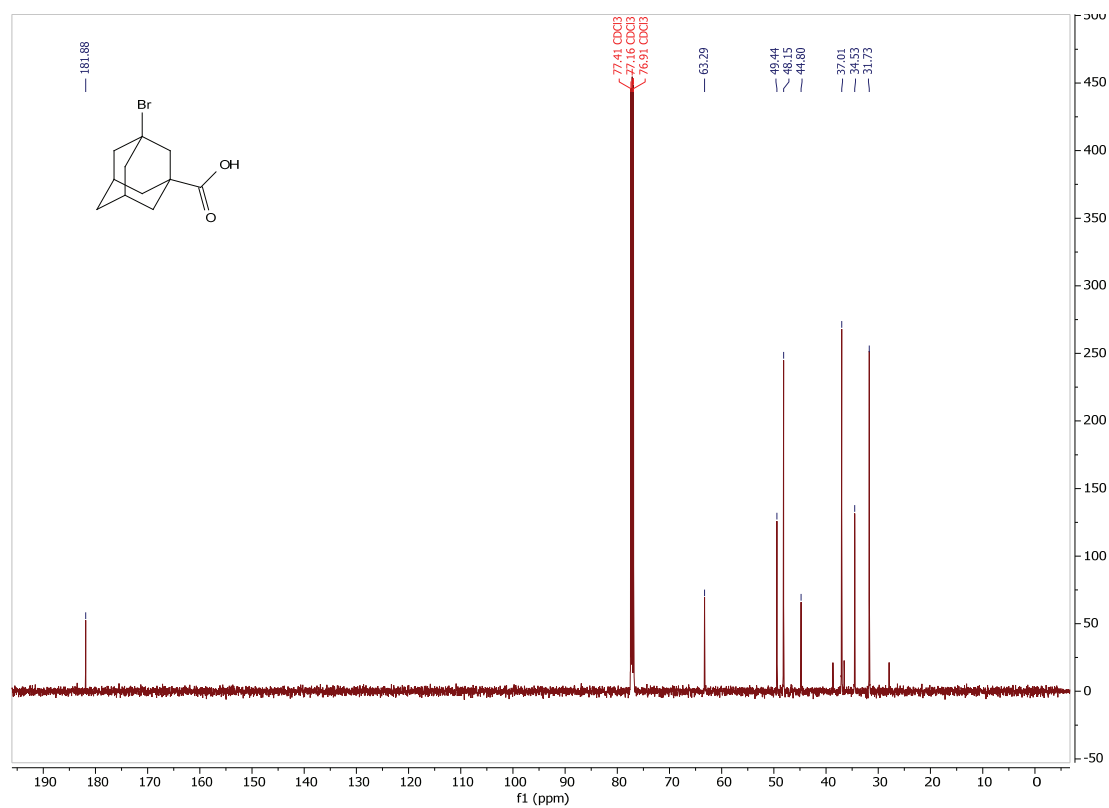
^{13}C NMR spectrum of N^1 -(2-(adamantan-1-yl)ethyl)- N^8 -(7-chloroquinolin-4-yl)octane-1,8-diamine (3)

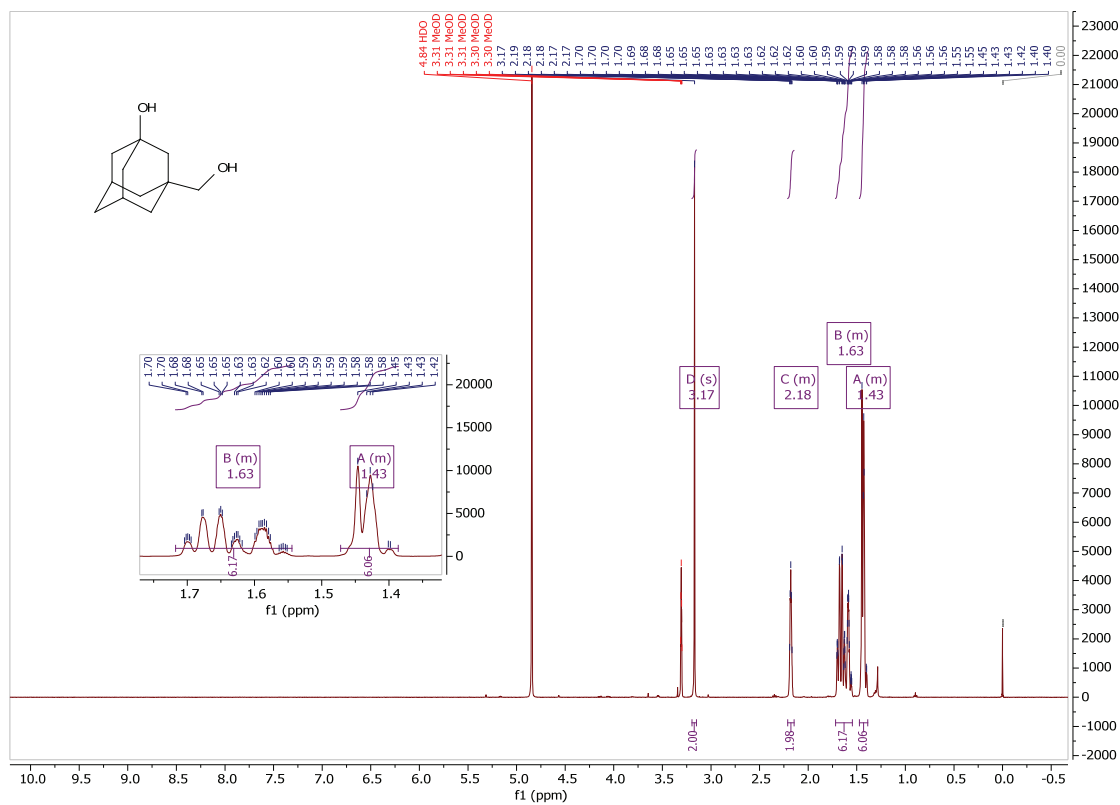


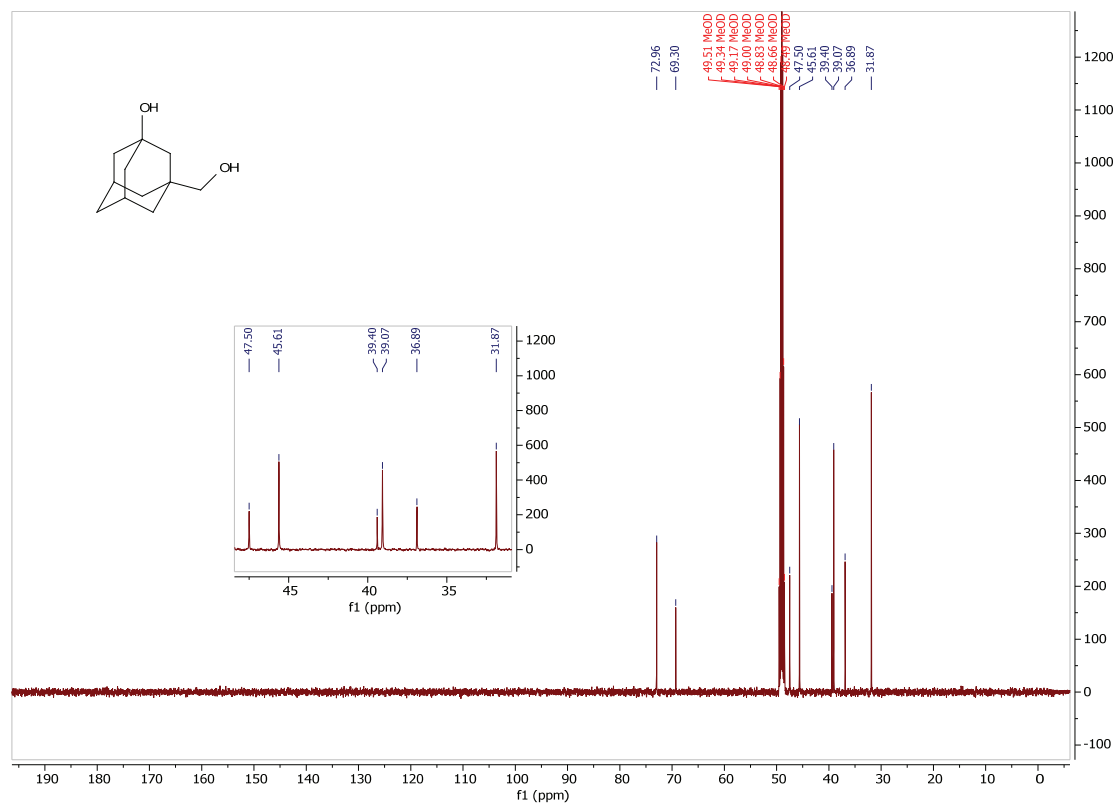
¹H NMR spectrum of 3-hydroxyadamantane-1-carboxylic acid (11)

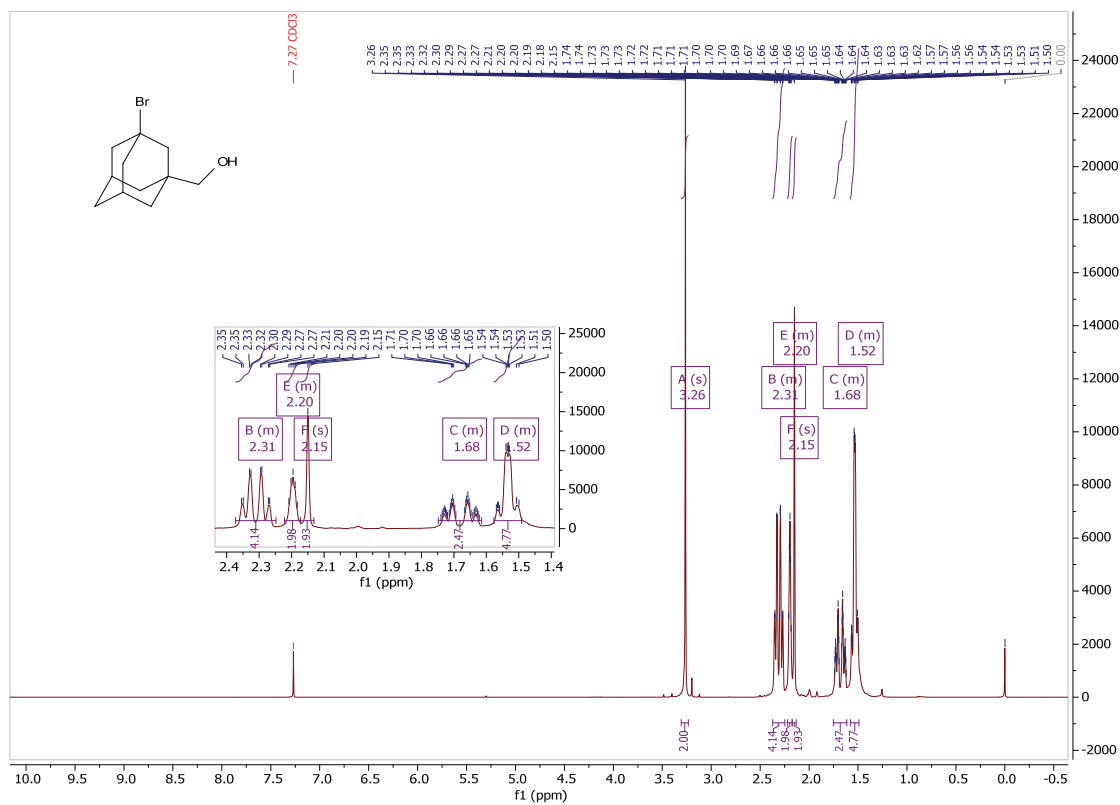
^{13}C NMR spectrum of 3-hydroxyadamantane-1-carboxylic acid (11)

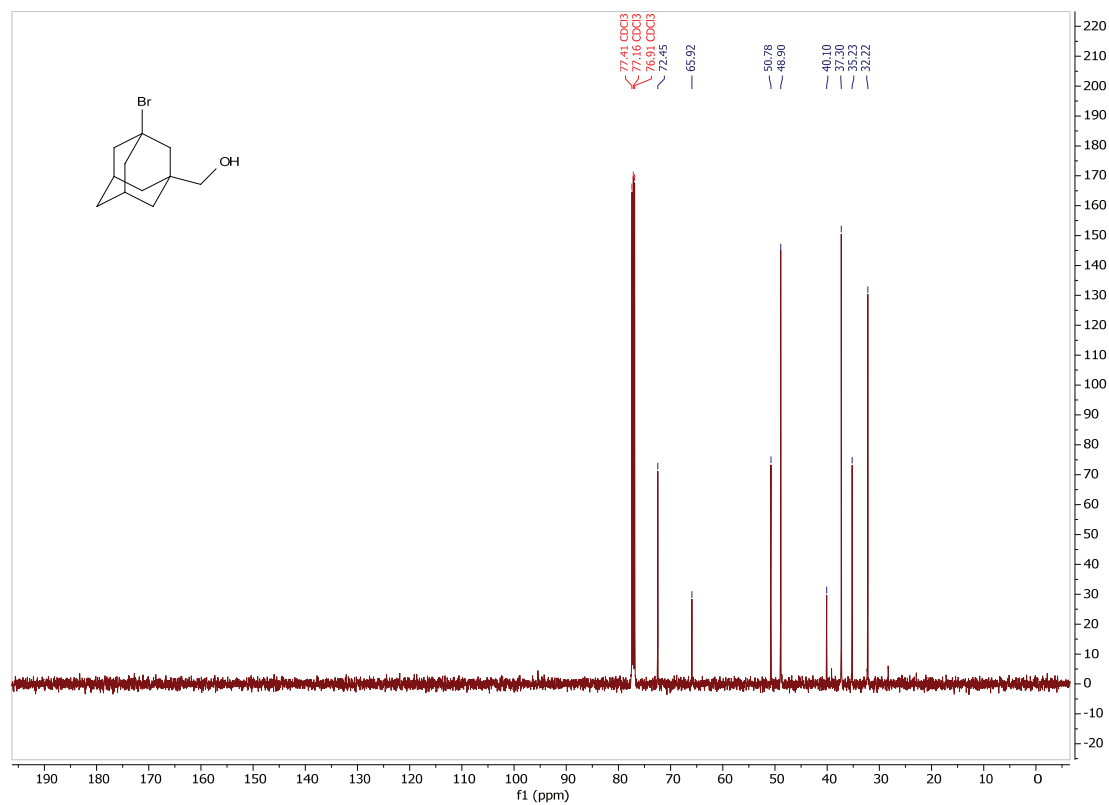
¹H NMR spectrum of 3-bromoadamantane-1-carboxylic acid (12)

^{13}C NMR spectrum of 3-bromoadamantane-1-carboxylic acid (12)

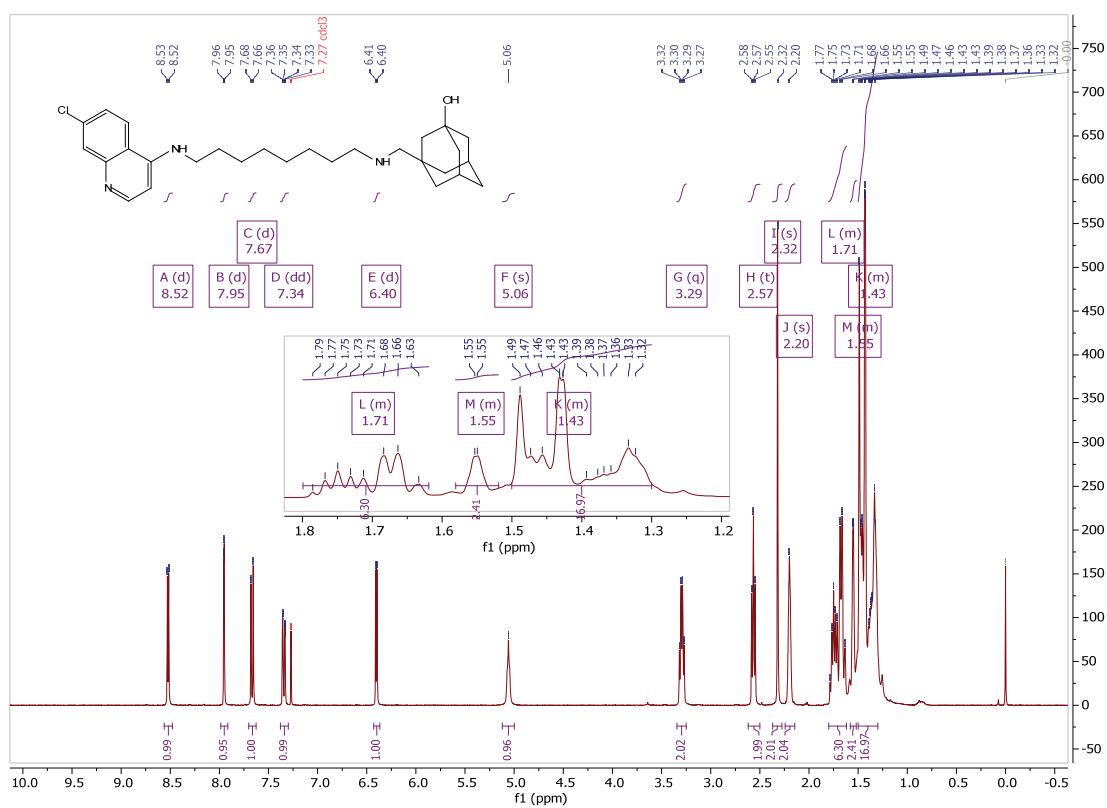
¹H NMR spectrum of 3-(hydroxymethyl)adamantan-1-ol (13)

^{13}C NMR spectrum of 3-(hydroxymethyl)adamantan-1-ol (13)

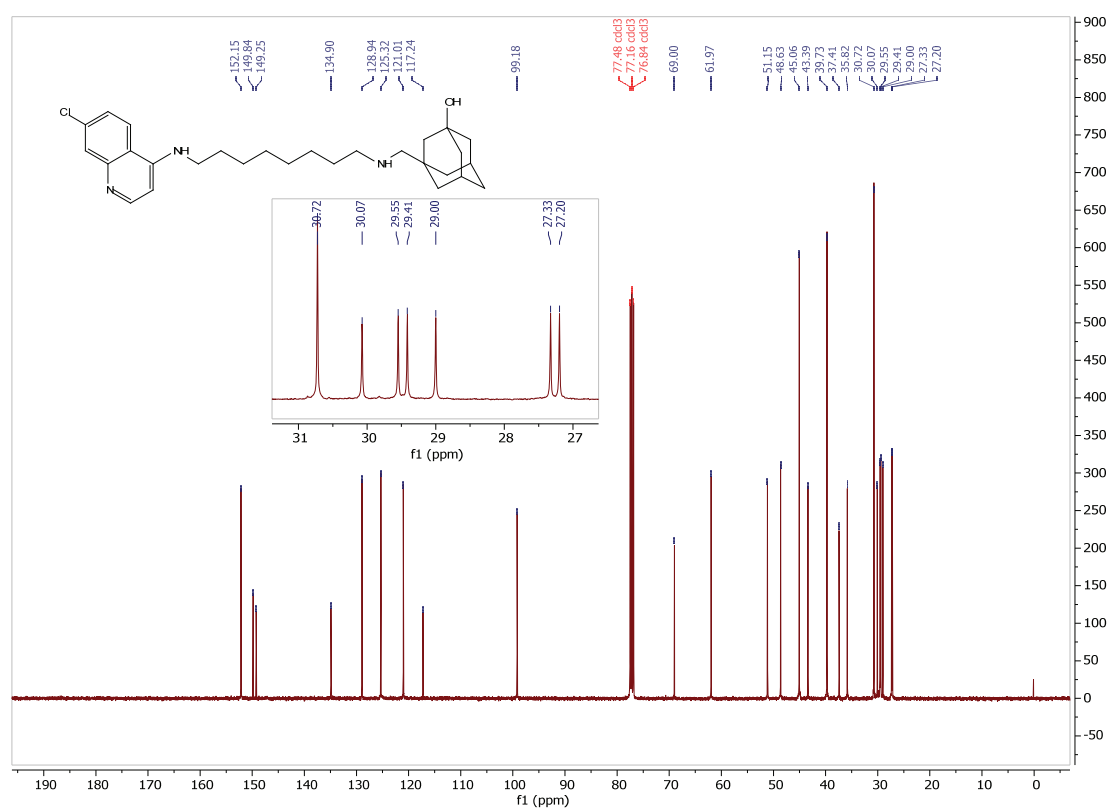
¹H NMR spectrum of (3-bromoadamantan-1-yl)methanol (14)

¹³C NMR spectrum of (3-bromoadamantan-1-yl)methanol (14)

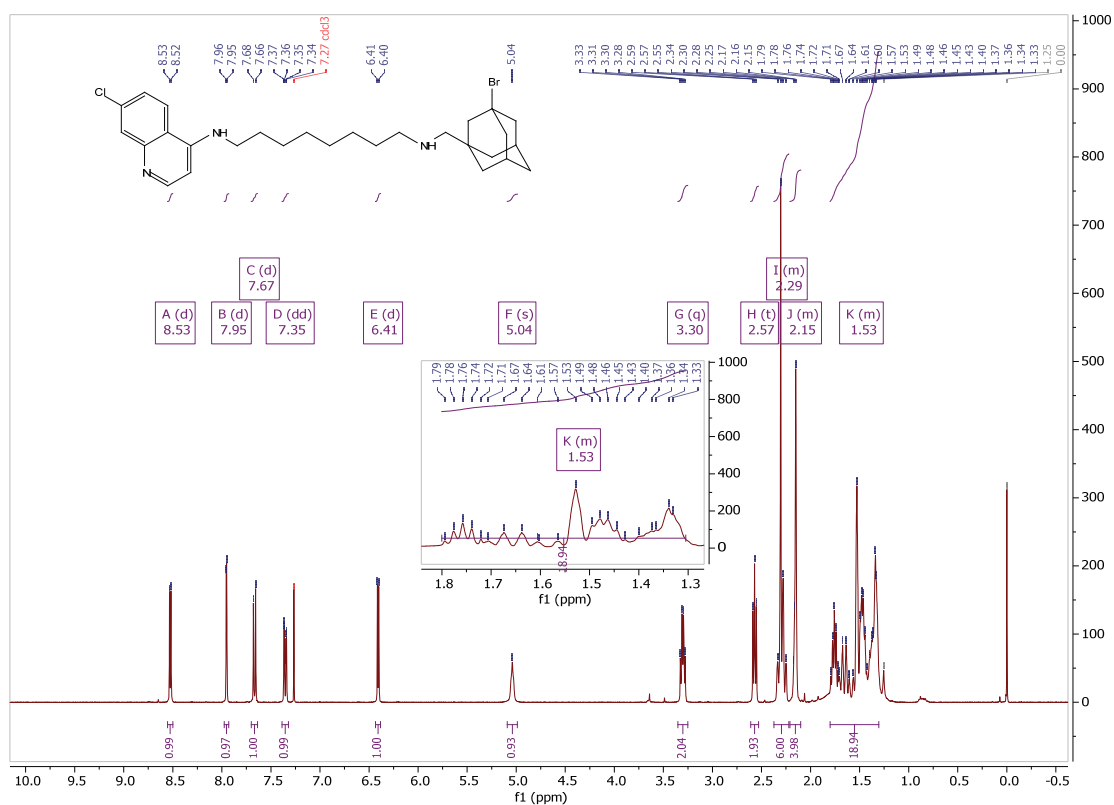
^1H NMR spectrum of 3-(((8-((7-chloroquinolin-4-yl)amino)octyl)amino)methyl)adamantan-1-ol (6)



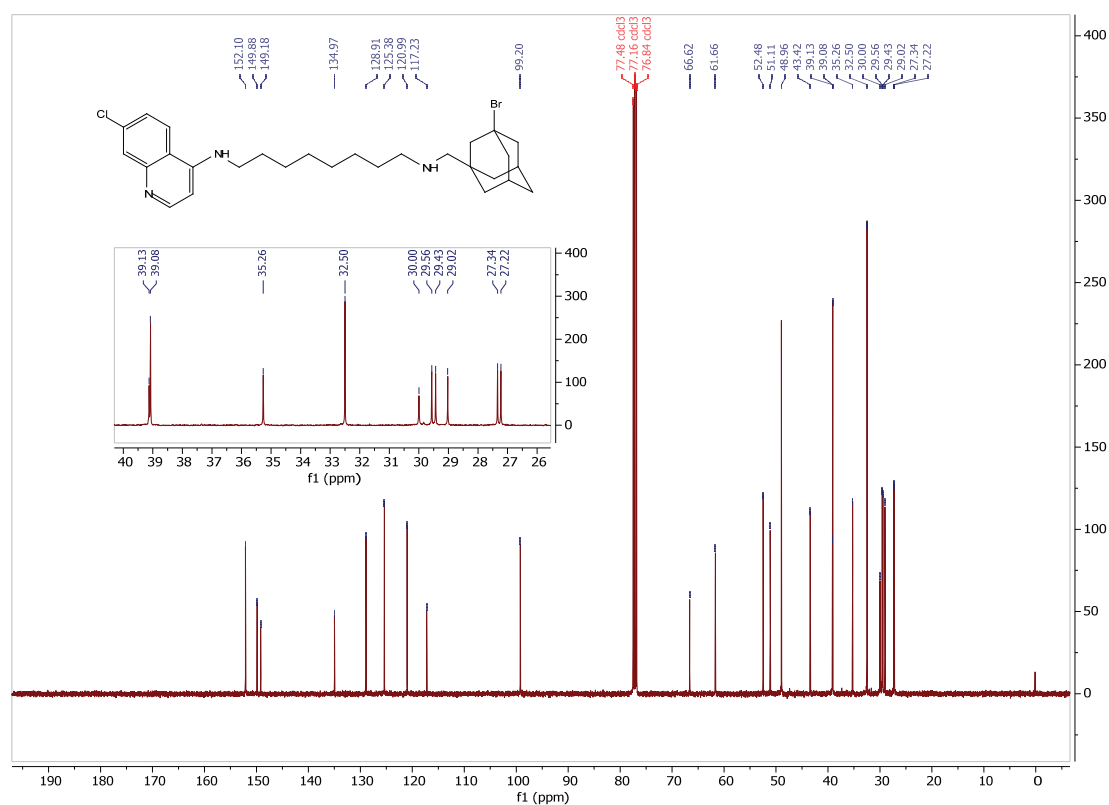
^{13}C NMR spectrum of 3-(((8-((7-chloroquinolin-4-yl)amino)octyl)amino)methyl)adamantan-1-ol (6)

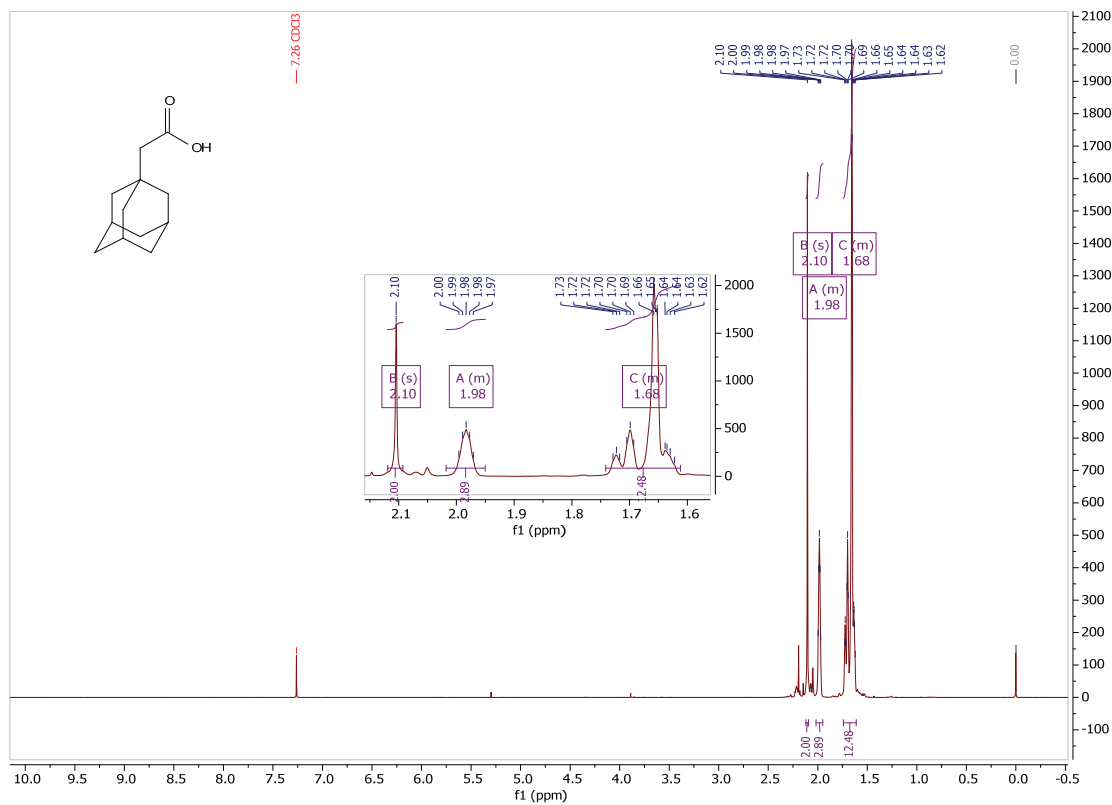


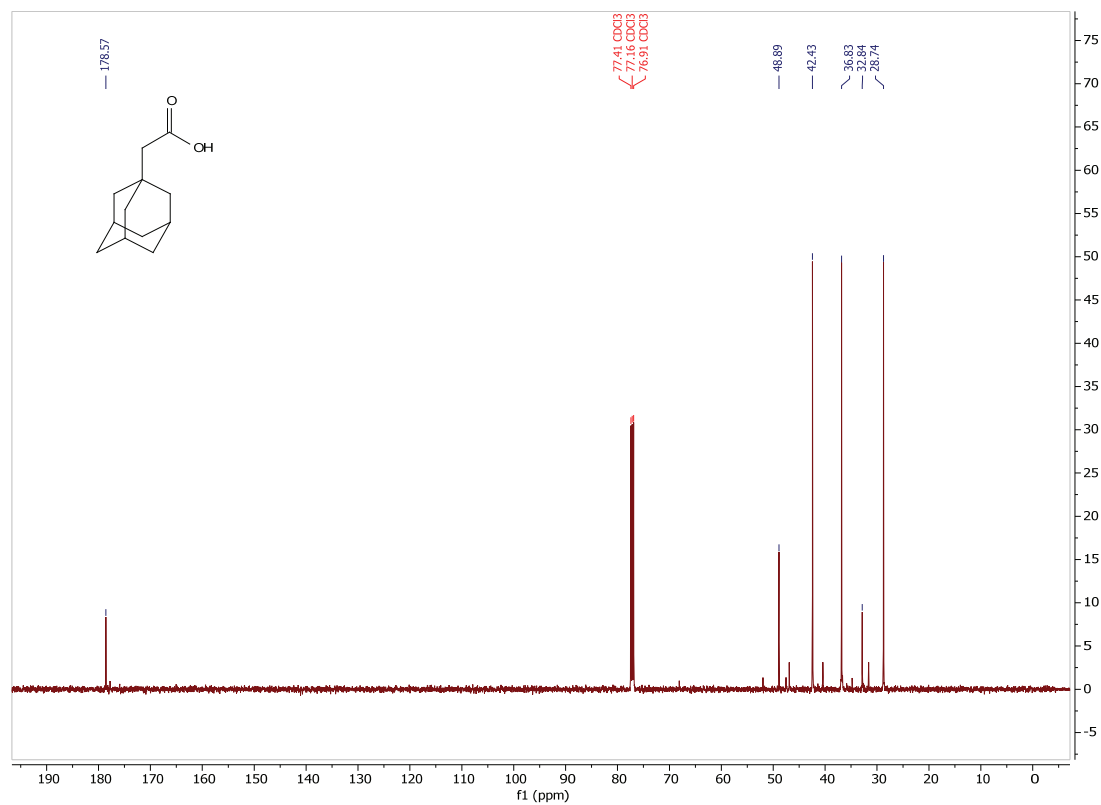
^1H NMR spectrum of N^1 -((3-bromoadamantan-1-yl)methyl)- N^8 -(7-chloroquinolin-4-yl)octane-1,8-diamine (7)

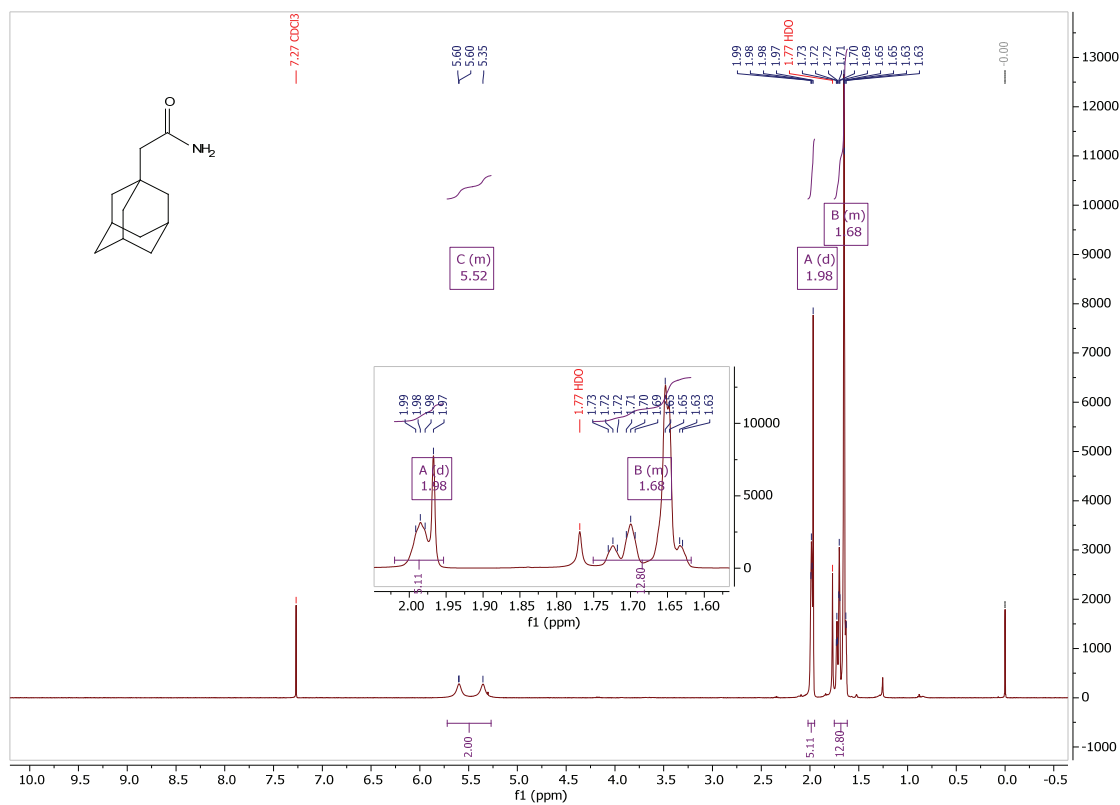


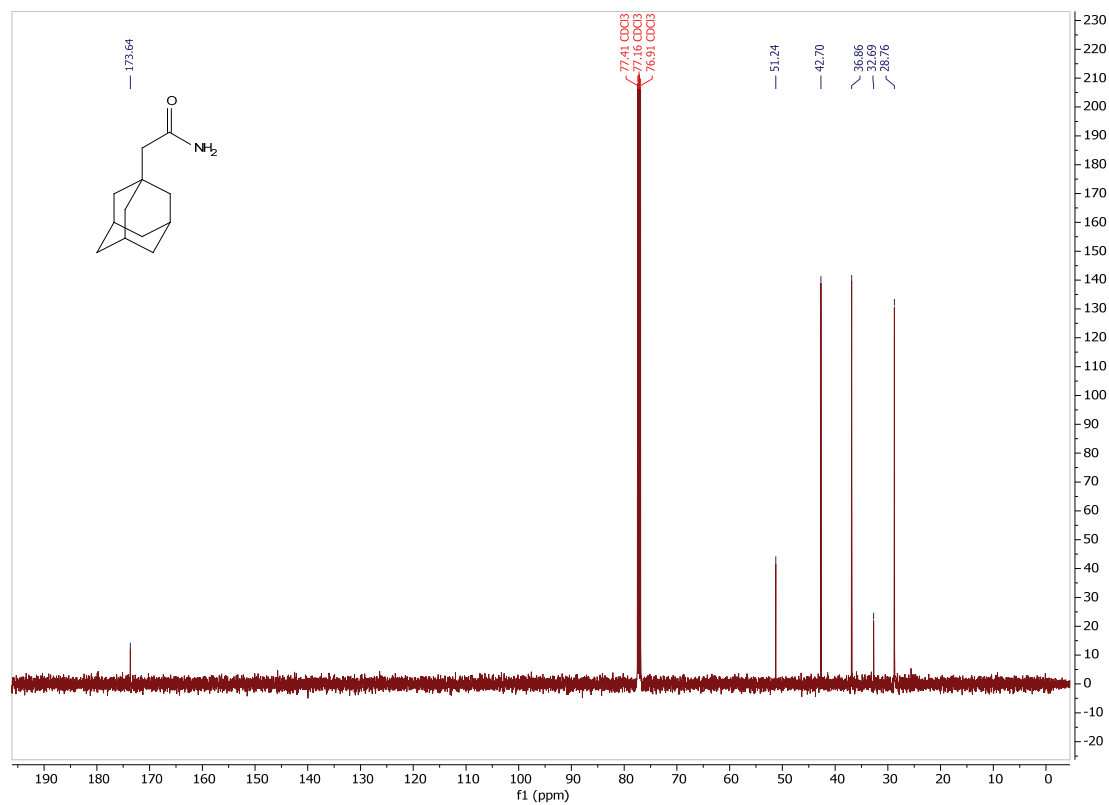
^{13}C NMR spectrum of N^1 -((3-bromoadamantan-1-yl)methyl)- N^8 -(7-chloroquinolin-4-yl)octane-1,8-diamine (7)

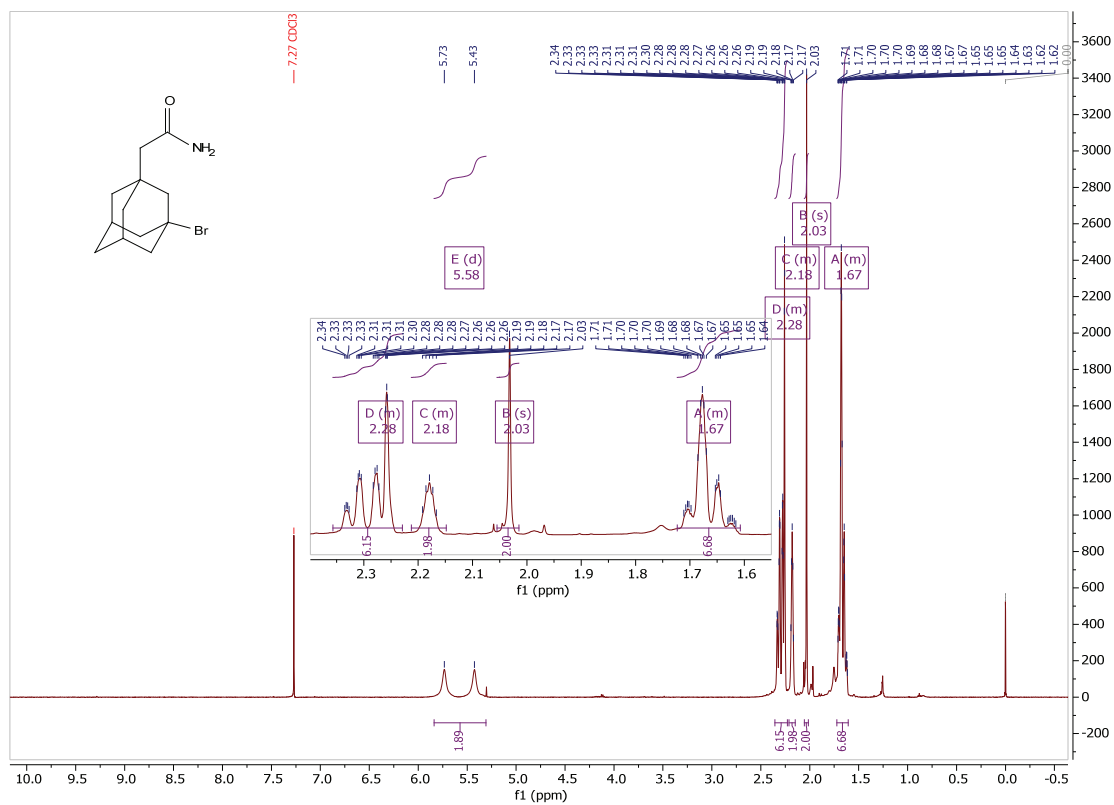


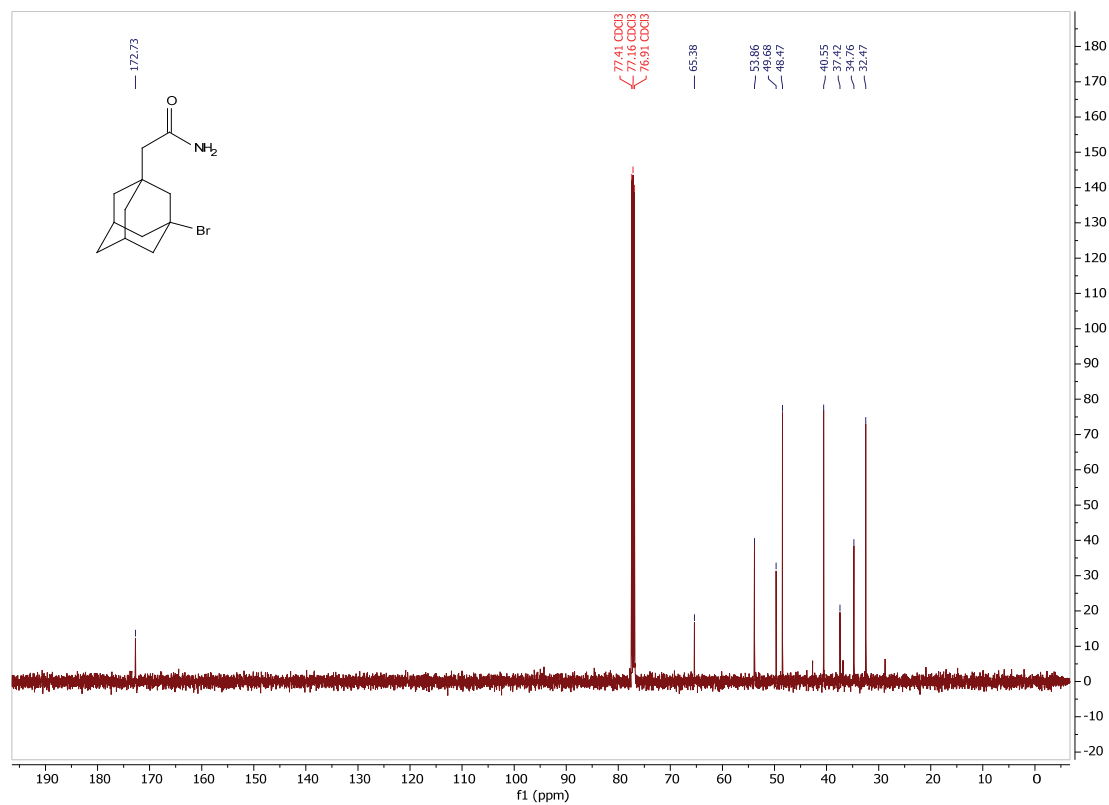
¹H NMR spectrum of 1-adamantaneacetic acid (18)

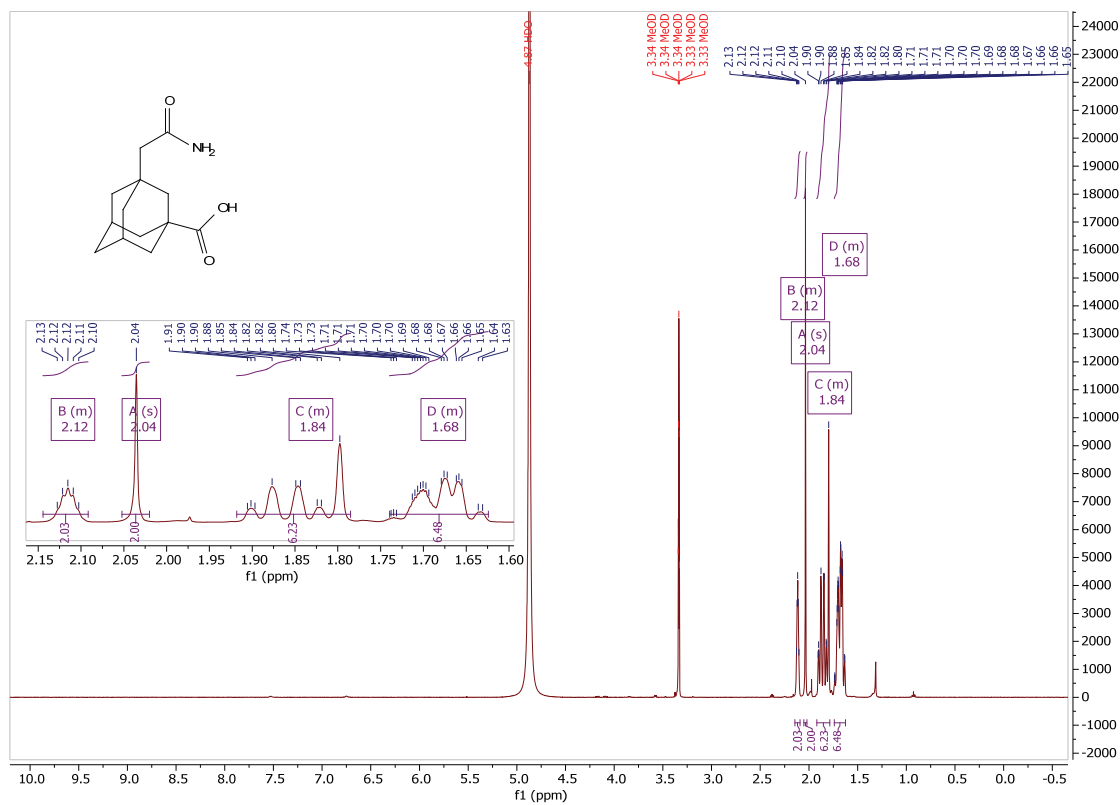
^{13}C NMR spectrum of 1-adamantaneacetic acid (18)

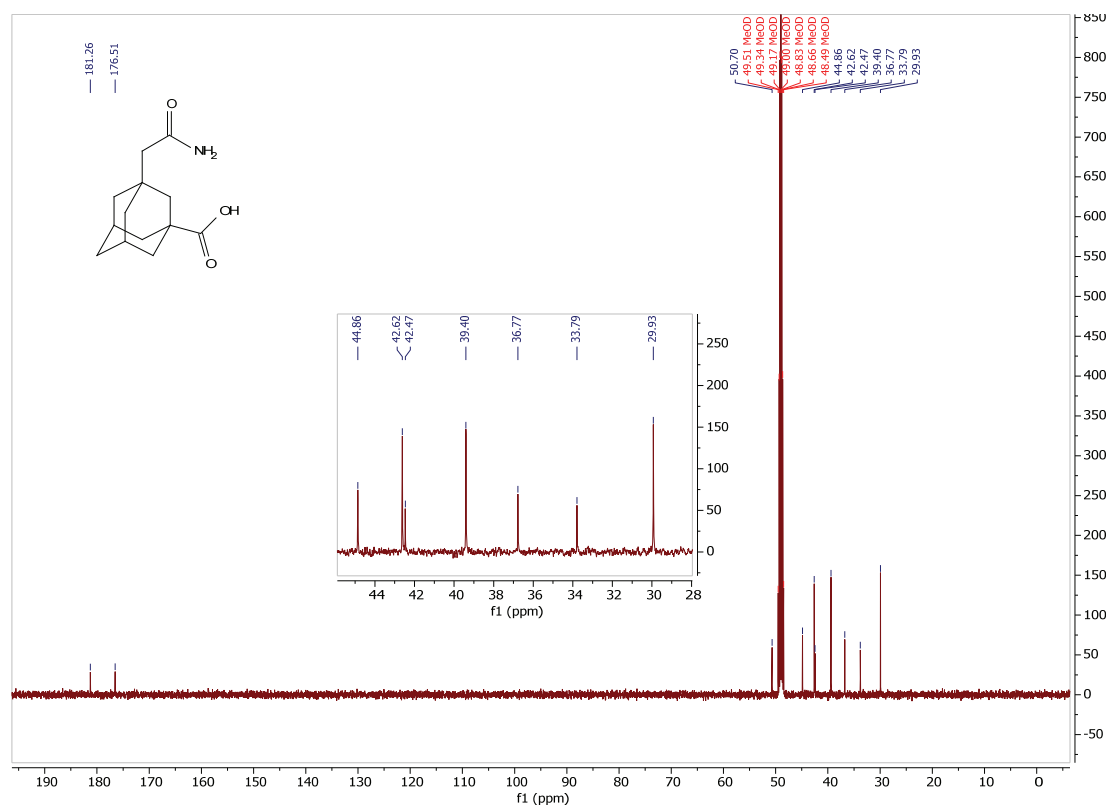
¹H NMR spectrum of 1-adamantaneacetamide (19)

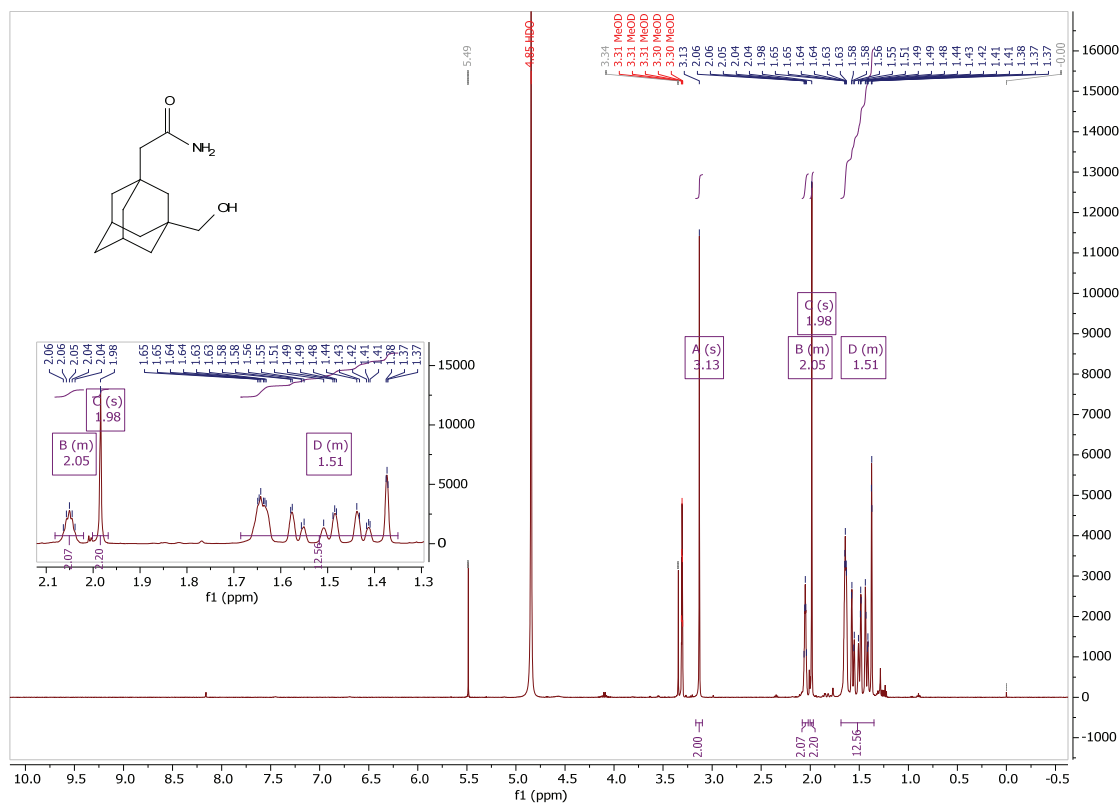
^{13}C NMR spectrum of 1-adamantaneacetamide (19)

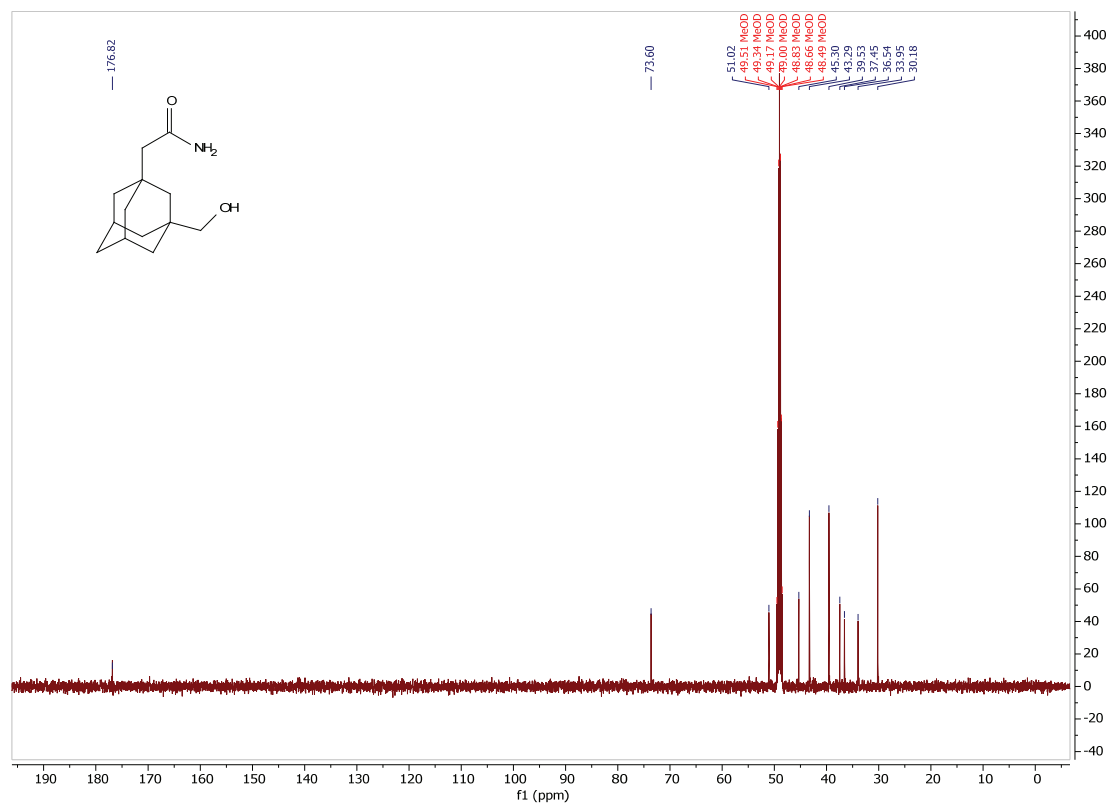
¹H NMR spectrum of 3-bromo-(1-adamantaneacetamide) (20)

¹³C NMR spectrum of 3-bromo-(1-adamantaneacetamide) (20)

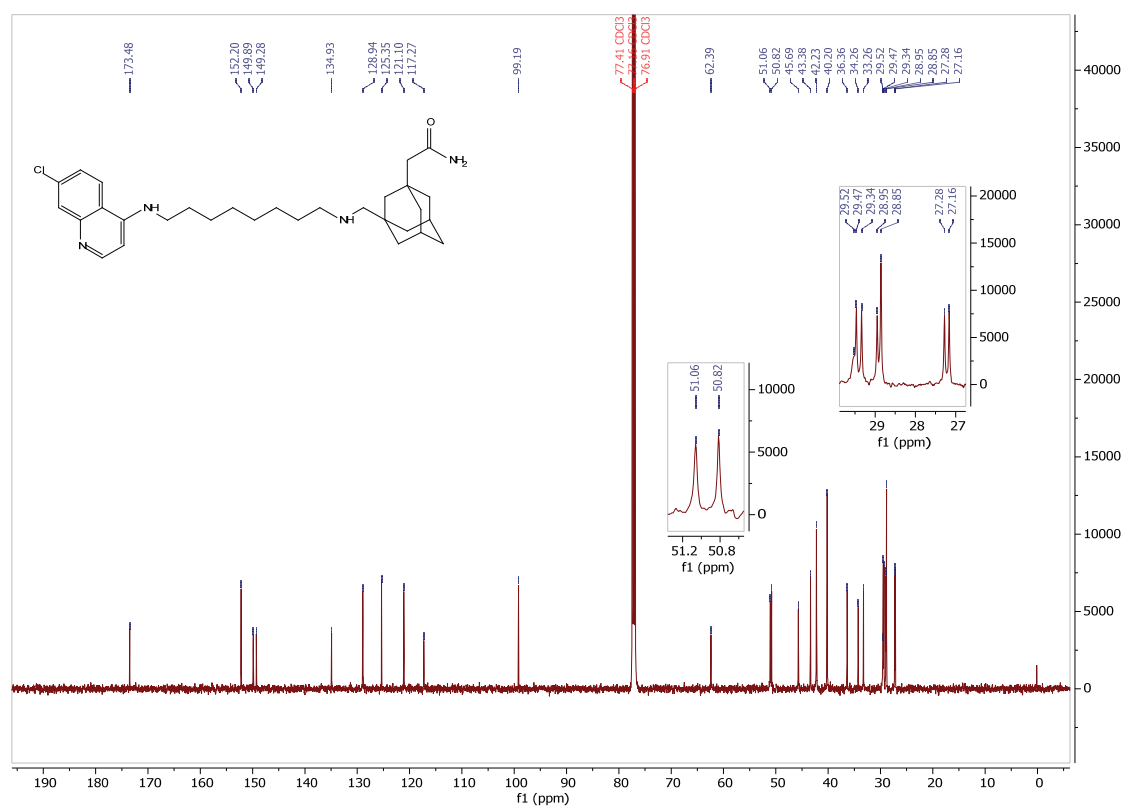
¹H NMR spectrum of 3-(2-amino-2-oxoethyl)adamantane-1-carboxylic acid (21)

^{13}C NMR spectrum of 3-(2-amino-2-oxoethyl)adamantane-1-carboxylic acid (21)

¹H NMR spectrum of 2-(3-(hydroxymethyl)adamantan-1-yl)acetamide (22)

^{13}C NMR spectrum of 2-(3-(hydroxymethyl)adamantan-1-yl)acetamide (22)

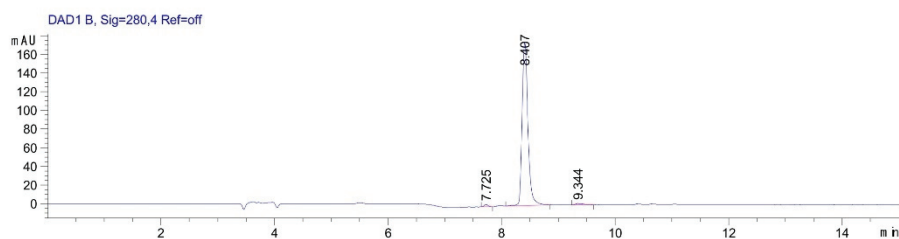
¹³C NMR spectrum of 2-(3-(((8-((7-chloroquinolin-4-yl)amino)octyl)amino)methyl)adamantan-1-yl)acetamide (8)



5. HPLC PURITY CHROMATOGRAMS

HPLC chromatogram of compound 3, method I

Sample Name: KBK45 Method I Compound 3
 =====
 Acq. Operator : SYSTEM Seq. Line : 18
 Sample Operator : SYSTEM
 Acq. Instrument : HPLC1260 Location : 48
 Inj Volume : 2.000 µl
 Method
 metoda 2.AC.N.M (Sequence Method)


 =====
 Fraction Information
 =====

No Fractions found.
 =====

 =====
 Area Percent Report
 =====

Sorted By : Signa
 Multiplier : 1.000
 Dilution : 1.000

Use Multiplier & Dilution Factor with ISTDs

Signal 2: DAD1 B, Sig=280,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.725	BB	0.0717	12.56595	2.73035	0.9881
2	8.407	BB	0.1113	1247.28442	174.62508	98.0745
3	9.344	BB	0.1150	11.92265	1.40566	0.9375

Totals : 1271.77302 178.76108

*** End of Report ***

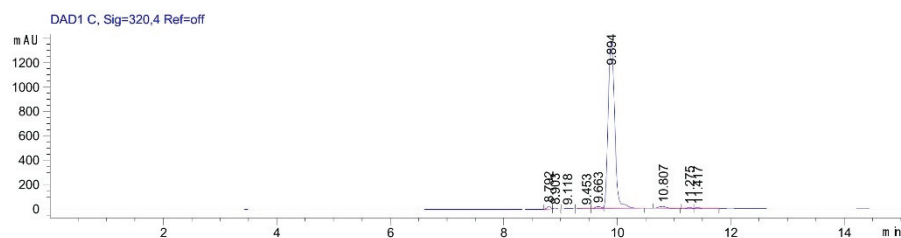
```

Sample Name: KBK45          Method II          Compound 3
=====
Acq. Operator   : SYSTEM                      Seq. Line :    2
Sample Operator : SYSTEM
Acq. Instrument : HPLC1260                    Location  :   48
                                           Inj Volume: 3.000 µl

Method
      metoda 1.M (Sequence Method)

Method Info      : Metoda 1 MeOH

```



No Fractions found.

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs
Signal 3: DAD1 C, Sig=320,4 Ref=off

Peak	RetTime	Type	Width	Area	Height	Area
#	[min]		[min]	[mAU*s]	[mAU]	%
1	8.792	BV	0.0698	100.77717	22.67707	0.8539
2	8.903	VB	0.0697	30.38930	6.59882	0.2575
3	9.118	BB	0.0939	22.18881	3.70206	0.1880
4	9.453	VB E	0.1123	11.00179	1.48812	0.0932
5	9.663	VV E	0.1145	118.22020	16.72628	1.0017
6	9.894	VB R	0.1342	1.12518e4	1364.23877	95.3386
7	10.807	BB	0.1291	160.95866	16.31722	1.3638
8	11.275	VB	0.1085	54.36814	8.08267	0.4607
9	11.417	VB	0.1095	52.22563	7.29542	0.4425

Totals : 1.18019e4 1447.12644

*** End of Report ***

HPLC chromatogram of compound 4, method III

Sample Name: KBK47 Method III Compound 4

=====

Acq. Operator : SYSTEM Seq. Line : 7

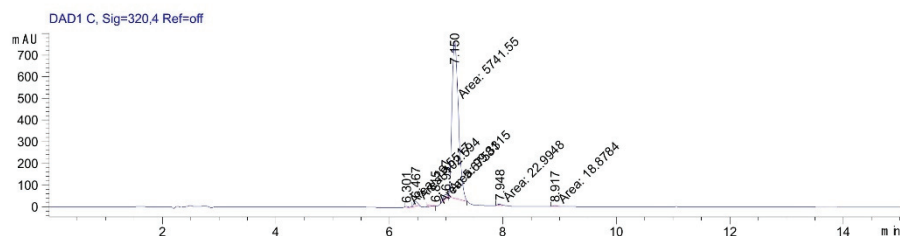
Sample Operator : SYSTEM

Acq. Instrument : HPLC1260 Location : 26

Inj Volume : 3.000 µl

Method

metoda 2.AC.N.M (Sequence Method)



=====

Fraction Information

=====

No Fractions found.

=====

=====

Area Percent Report

=====

Sorted By : Signal

Multiplier : 1.0000

Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 3: DAD1 C, Sig=320,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.301	MM	0.0656	19.55173	4.96475	0.3253
2	6.467	MM	0.0816	102.59441	20.94633	1.7069
3	6.815	MM	0.0360	5.67581	2.62664	0.0944
4	6.997	MM	0.0815	99.33145	20.30647	1.6526
5	7.150	MM	0.1318	5741.55273	726.23987	95.5241
6	7.948	MM	0.0742	22.99480	5.16225	0.3826
7	8.917	MM	0.0927	18.87844	3.39475	0.3141

Totals : 6010.57937 783.64105

=====

*** End of Report ***

HPLC chromatogram of compound 4, method IV

Sample Name: KBK47 Method IV Compound 4

=====

Acq. Operator : SYSTEM Seq. Line : 41

Sample Operator : SYSTEM

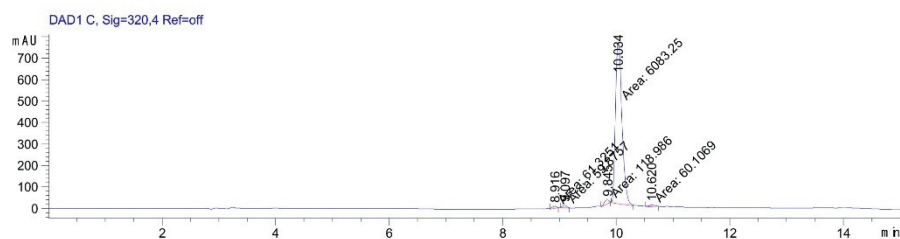
Acq. Instrument : HPLC1260 Location : 26

Inj Volume : 3.000 µl

Method

metoda 1.M (Sequence Method)

Method Info : Metoda 1 MeOH



=====

Fraction Information

=====

No Fractions found.

=====

=====

Area Percent Report

=====

Sorted By : Signa

Multiplier : 1.000

Dilution : 1.000

Use Multiplier & Dilution Factor with ISTDs

Signal 3: DAD1 C, Sig=320,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.916	MM	0.0993	61.32508	10.29342	0.9607
2	9.097	MM	0.0926	59.87572	10.78159	0.9380
3	9.845	MM	0.1056	118.98644	18.78357	1.8640
4	10.034	MM	0.1347	6083.24805	752.96307	95.2958
5	10.620	MM	0.1203	60.10685	8.32531	0.9416

Totals : 6383.54214 801.14698

=====

*** End of Report ***

HPLC chromatogram of compound 5, method I

Sample Name: KBK48 Methoda I Compound 5

=====

Acq. Operator : SYSTEM Seq. Line : 12

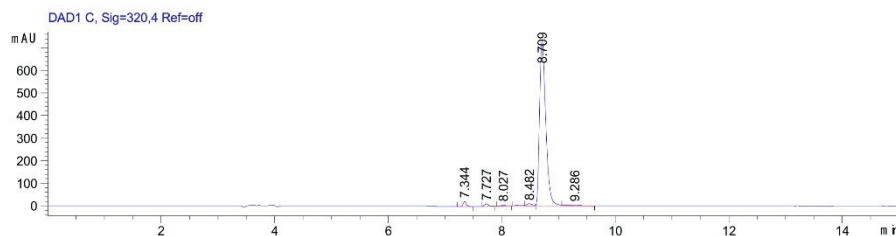
Sample Operator : SYSTEM

Acq. Instrument : HPLC1260 Location : 42

Inj Volume : 2.000 µl

Method

metoda 2.AC.N.M (Sequence Method)



=====

Fraction Information

=====

No Fractions found.

=====

=====

Area Percent Report

=====

Sorted By : Signal

Multiplier : 1.0000

Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 3: DAD1 C, Sig=320,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.344	BB	0.0593	87.20990	22.47513	1.4465
2	7.727	BB	0.0777	52.47802	10.61152	0.8704
3	8.027	BB	0.0868	25.87752	4.51626	0.4292
4	8.482	VV E	0.1078	67.10393	9.34007	1.1130
5	8.709	VV R	0.1229	5759.69629	735.13507	95.5346
6	9.286	VB E	0.1541	36.54370	3.08680	0.6061

Totals : 6028.90936 785.16485

=====

*** End of Report ***

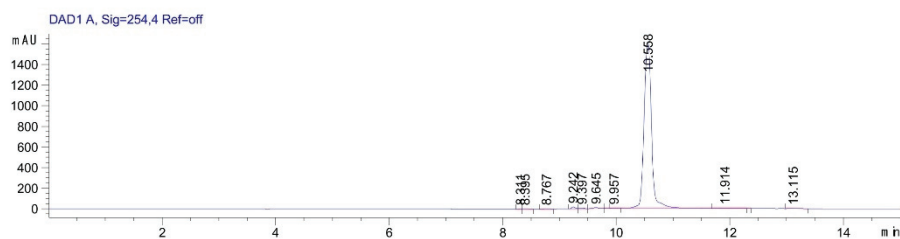
```

Sample Name: KBK48                      Methoda II          Compound 5
=====
Acq. Operator   : SYSTEM                      Seq. Line   : 34
Sample Operator : SYSTEM
Acq. Instrument : HPLC1260                  Location    : 42
                                           Inj Volume  : 3.000 µl

Method
      metoda 1.M (Sequence Method)

Method Info    : Metoda 1 MeOH

```



No Fractions found.

```
Sorted By      :      Signal
Multiplier    :      1.0000
Dilution      :      1.0000
Use Multiplier & Dilution Factor with ISTDs
```

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.311	BV	0.0524	5.83001	1.77242	0.0388
2	8.395	BV	0.0748	25.67034	5.08937	0.1706
3	8.767	BB	0.0746	14.68180	2.92145	0.0976
4	9.242	BV	0.0710	86.24202	18.30317	0.5733
5	9.397	BV	0.0727	42.73519	9.10699	0.2841
6	9.645	BB	0.0963	66.82705	9.95200	0.4442
7	9.957	BV E	0.0935	13.95853	2.41147	0.0928
8	10.558	VV R	0.1402	1.470684	1615.26794	97.7614
9	11.914	BV E	0.1537	60.21075	5.25358	0.4002
10	13.115	BB	0.1438	20.61539	2.00828	0.1370

Totals :	1.50436e4	1672.08669
----------	-----------	------------

*** End of Report ***

HPLC chromatogram of compound 6, method III

Sample Name: KBK64 Method III Compound 6

=====

Acq. Operator : SYSTEM Seq. Line : 14

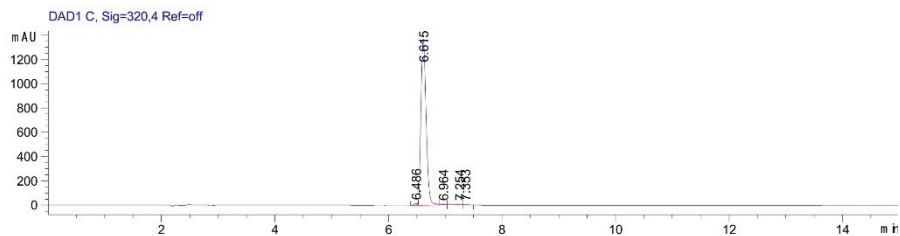
Sample Operator : SYSTEM

Acq. Instrument : HPLC1260 Location : 33

Inj Volume : 3.000 µl

Method

metoda 2.AC.N.M (Sequence Method)



=====

Fraction Information

=====

No Fractions found.

=====

=====

Area Percent Report

=====

Sorted By : Signal

Multiplier : 1.0000

Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 3: DAD1 C, Sig=320,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.486	BV E	0.0613	59.80951	15.40364	0.6924
2	6.615	VV R	0.0962	8491.18359	1372.08960	98.3058
3	6.964	VB E	0.0625	9.22906	2.31716	0.1068
4	7.254	VV R	0.1028	39.71161	5.59855	0.4598
5	7.353	VB	0.0866	37.58918	6.38948	0.4352

Totals : 8637.52296 1401.79843

=====

*** End of Report ***

HPLC chromatogram of compound 6, method IV

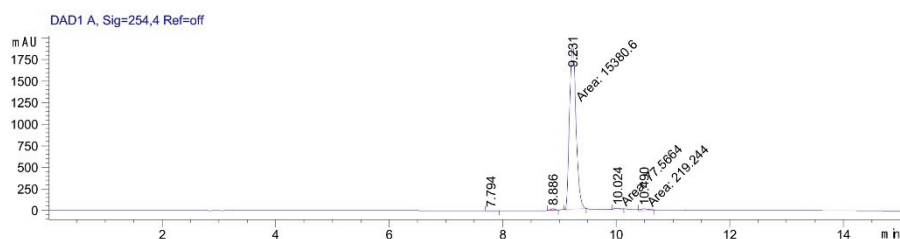
Sample Name: KBK64 Method IV Compound 6

=====

Acq. Operator : SYSTEM	Seq. Line : 48
Sample Operator : SYSTEM	
Acq. Instrument : HPLC1260	Location : 33
Inj Volume : 3.000 µl	

Method
metoda 1.M (Sequence Method)

Method Info : Metoda 1 MeOH



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Fraction Information

=====

No Fractions found.

=====

=====

Area Percent Report

=====

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.794	BB	0.0972	6.76740	1.04925	0.0429
2	8.886	BB	0.0930	89.83051	15.64876	0.5695
3	9.231	MM	0.1336	1.53806e4	1918.15881	97.5060
4	10.024	MM	0.1306	77.56643	9.89686	0.4917
5	10.490	MM	0.1917	219.24388	19.06480	1.3899

Totals : 1.57741e4 1963.81848

=====

*** End of Report ***

HPLC chromatogram of compound 7, method III

Sample Name: KBK63b

Method III

Compound 7

Acq. Operator : SYSTEM

Sample Operator : SYSTEM

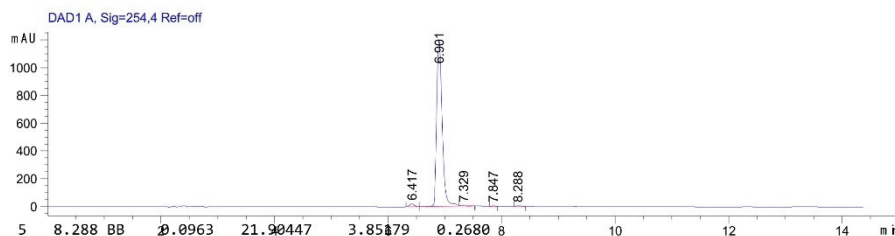
Acq. Instrument : HPLC1260

Location : 24

Inj Volume : 3.000 µl

Acq. Method : C:\ChemStation\1\Methods\HPLC cistoca metoda 2.ACN.M

Analysis Method : C:\ChemStation\1\Methods\DEF_LC.M



Fraction Information

No Fractions found.

Area Percent Report

Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.417	BV	0.0911	120.12967	20.90011	1.4696
2	6.901	VV R	0.1040	8007.90674	1197.37476	97.9653
3	7.329	VB E	0.1134	16.89939	2.15666	0.2067
4	7.847	BV	0.0733	7.38698	1.55718	0.0904
5	8.288	BB	0.0963	21.90447	3.85179	0.2680

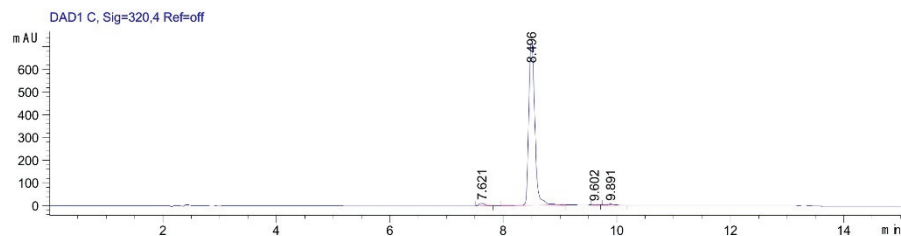
*** End of Report ***

HPLC chromatogram of compound 7, method IV

Sample Name: KBK63b Method IV Compound 7

```
=====
Acq. Operator   : SYSTEM
Sample Operator : SYSTEM
Acq. Instrument : HPLC1260                      Location :   24

                                           Inj Volume : 3.000 µl
Acq. Method    : C:\ChemStation\1\Methods\HPLC cistoca metoda 1.M
                                           (modified after loading)
Analysis Method : C:\ChemStation\1\Methods\DEF_LC.M
```



```
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Fraction Information
=====
```

No Fractions found.

```
=====
Area Percent Report
=====
```

```
Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
Use Multiplier & Dilution Factor with ISTDs

Signal 3: DAD1 C, Sig=320,4 Ref=off
```

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.621	BB	0.1206	76.21922	10.51346	1.4169
2	8.496	BB	0.1123	5272.46436	729.43896	98.0116
3	9.602	BB	0.0836	5.84354	1.18304	0.1086
4	9.891	BB	0.0962	24.90395	4.02220	0.4629

Totals : 5379.43106 745.15767

```
=====
*** End of Report ***
=====
```

HPLC chromatogram of compound 8, method III

Sample Name: KBK68 Method III Compound 8

=====

Acq. Operator : SYSTEM Seq. Line : 18

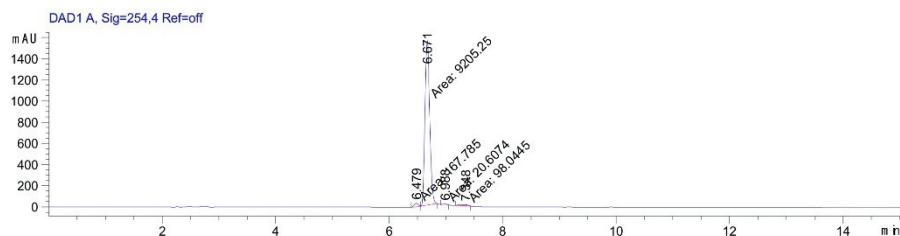
Sample Operator : SYSTEM

Acq. Instrument : HPLC1260 Location : 37

Inj Volume : 3.000 µl

Method

metoda 2.AC.N.M (Sequence Method)



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Fraction Information

=====

No Fractions found.

=====

=====

Area Percent Report

=====

Sorted By : Signal

Multiplier : 1.0000

Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.479	MM	0.0823	167.78525	33.99279	1.7677
2	6.671	MM	0.0984	9205.25488	1558.82935	96.9822
3	6.988	MM	0.0570	20.60745	6.02871	0.2171
4	7.348	MM	0.1513	98.04446	10.80194	1.0330

Totals : 9491.69204 1609.65278

=====

*** End of Report ***

HPLC chromatogram of compound 8, method IV

Sample Name: KBK68 Method IV Compound 8

=====

Acq. Operator : SYSTEM Seq. Line : 52

Sample Operator : SYSTEM

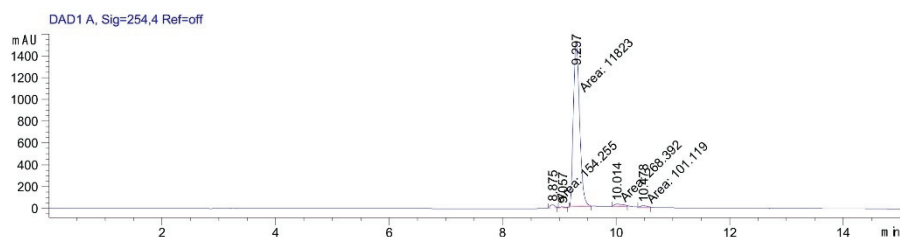
Acq. Instrument : HPLC1260 Location : 37

Inj Volume : 3.000 µl

Method

metoda 1.M (Sequence Method)

Method Info : Metoda 1 MeOH



=====

Fraction Information

=====

No Fractions found.

=====

=====

Area Percent Report

=====

Sorted By : Signal

Multiplier : 1.0000

Dilution : 1.0000

Use Multiplier & Dilution Factor with ISTDs

Signal 1: DAD1 A, Sig=254,4 Ref=off

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.875	MM	0.0941	154.25528	27.31053	1.2453
2	9.057	VB	0.1015	40.69626	6.29104	0.3285
3	9.297	MM	0.1302	1.18230e4	1513.76807	95.4433
4	10.014	MM	0.1856	268.39194	24.10622	2.1666
5	10.478	MM	0.1172	101.11902	14.38363	0.8163

Totals : 1.23874e4 1585.85949

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*** End of Report ***

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6. REFERENCES

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