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SUPPLEMENTARY MATERIAL TO

Hybrids of 4-aminoquinolines and adamantane as inhibitors of AChE

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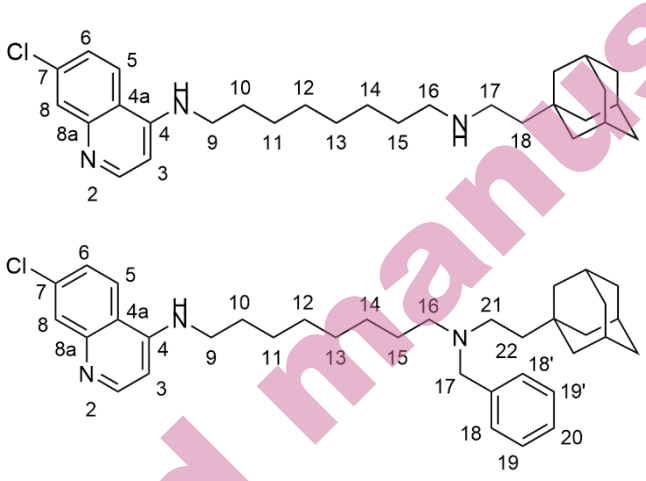


N^1-Benzyl-N^8-(7-chloroquinolin-4-yl)octane-1,8-diamine (2).

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, CD_3OD, 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× -CH_2, 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 $NaHCO_3$, 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 anh. Na_2SO_4. 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, $CDCl_3$, 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, -N*H*), 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× -C*H*(Ad)), 1.78 – 1.56 (m, 8H, 3× -CH_2(Ad) and -CH_2 H-10), 1.50 – 1.25 (m, 18H, 3× -CH_2(Ad) and 6× -CH_2 H-(11-15) and H-22). ^{13}C NMR (100

MHz, $CDCl_3$, 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, CD_3OD, 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 CD_3OD), 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× -CH_2).

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, CD_3OD, 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× -CH_2(Ad) and -CH_2 H-10), 1.61 – 1.30 (m, 16H, 3× -CH_2(Ad) and 5× -CH_2).

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 $NaBH_3CN$ (9.7 mg, 0.1544 mmol) and $ZnCl_2$ (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 $NaHCO_3$ 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 anh. Na_2SO_4. 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, $CDCl_3$, 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× -CH_2(Ad)), 1.51 (d, J = 2.2 Hz, 6H, 3× -CH_2(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). ^{13}C NMR (125 MHz, $CDCl_3$, 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 anh. Na_2SO_4. The solvent was evaporated and the product was isolated after chromatographic purification (dry-flash chromatography, silica gel, gradient prepared from DCM and mixture [MeOH/NH_3(aq)=9/1], then multiple preparative thin-layer chromatography, silica gel, EA/MeOH/NH_3(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, $CDCl_3$, 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-N*H*), 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× -C*H*(Ad)), 1.79 – 1.58 (m, 8H, 3× -CH_2(Ad) and -CH_2 H-10), 1.54 – 1.40 (m, 10H, 3× -CH_2(Ad) and 2× -CH_2 H-15 and H-11), 1.40 – 1.24 (m, 8H, H-18 and 3× -CH_2 H-(12-14)). ^{13}C NMR (100 MHz, $CDCl_3$, 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 $[C_{29}H_{42}ClN_3+H]^+$ 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% H_2SO_4 (4 mL) and 65% HNO_3 (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, CD_3OD, δ) 2.25 – 2.19 (m, 2H, 2× -C*H*), 1.84 – 1.74 (m, 6H, 3× -CH_2), 1.73 – 1.65 (m, 4H, 2× -CH_2), 1.64 – 1.59 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, CD_3OD, 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, $CDCl_3$, δ) 2.49 (s, 2H, -CH_2), 2.37 – 2.27 (m, 4H, 2× -CH_2), 2.25 – 2.20 (m, 2H, 2× -C*H*), 1.91 (d, *J* = 2.9 Hz, 4H, 2× -CH_2), 1.75 – 1.67 (m, 2H, -CH_2). ^{13}C NMR (125 MHz, $CDCl_3$, 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), Et_3N (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 $NaBH_4$ (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 anh. 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, Mp = 108-112 °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, -C*H*$_2$OH), 2.21 – 2.15 (m, 2H, 2 -C*H*), 1.72 – 1.54 (m, 6H, 3× -C*H*$_2$), 1.47 – 1.39 (m, 6H, 3× -C*H*$_2$). ^{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) $[M]^+$, 151.1 (100) $[M - CH_2OH]^+$, 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 anh. 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, Mp = 73-77 °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, -C*H*$_2$OH), 2.37 – 2.25 (m, 4H, 2× -C*H*$_2$), 2.22 – 2.17 (m, 2H, 2× -C*H*), 2.15 (s, 2H, -C*H*$_2$), 1.75 – 1.61 (m, 2H, -C*H*$_2$), 1.58 – 1.49 (m, 4H, 2× -C*H*$_2$). ^{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) $[M - CH_2OH]^+$, 165.1 (100) $[M - Br]^+$, 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 anh. 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-N*H*), 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× -C*H*(Ad)), 1.80 – 1.62 (m, 6H, 2× -CH_2(Ad) and -CH_2 H-10), 1.58 – 1.52 (m, 2H, -CH_2(Ad)), 1.50 – 1.30 (m, 16H, 3× -CH_2(Ad) and 5× -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-N*H*), 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× -CH_2(Ad)), 2.21 – 2.10 (m, 4H, 2× -C*H*(Ad) and -CH_2(Ad)), 1.80 – 1.30 (m, 18H, 3× –CH_2(Ad) and 6× -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 anh. 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× -C*H*), 1.74 – 1.61 (m, 12H, 6× -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 anh. 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, Mp = 168-170 °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, -NH_2), 2.02 – 1.95 (m, 5H, 2× -C*H* and -CH_2CONH$_2$), 1.75 – 1.62 (m, 12H, 6 -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) $[M]^+$, 135.1 (100) $[M - CH_2CONH_2]^+$, 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 anh. 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 °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 anh. 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, Mp = 104-110 °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 Hz, 2H, -NH_2), 2.36 – 2.23 (m, 6H, 3× -CH_2), 2.21 – 2.15 (m, 2H, 2× -C*H*), 2.03 (s, 2H, -CH_2CONH$_2$), 1.72 – 1.61 (m, 6H, 3× -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) $[M - Br]^+$, 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 °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, Mp = 224-228 °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× -C*H*), 2.04 (s, 2H, -CH_2CONH$_2$), 1.92 – 1.79 (m, 6H, 3× -CH_2), 1.74 – 1.62 (m, 6H, 3× -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) $[2M - H]^-$, 236.41 (50) $[M - H]^-$.

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

A solution of **21** (1.025 g, 4.3194 mmol) in DCM (23.5 mL), with Et_3N (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 $NaBH_4$ (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 $NaHCO_3$, 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, CD_3OD, δ) 3.13 (s, 2H, -C*H*$_2$OH), 2.09 – 2.01 (m, 2H, 2× -C*H*), 1.98 (s, 2H, -C*H*$_2$CONH$_2$), 1.70 – 1.33 (m, 12H, 6× -C*H*$_2$). ^{13}C NMR (125 MHz, CD_3OD, 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) $[M - CH_2OH]^+$, 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 $NaBH_4$ (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, $CDCl_3$, 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, -N*H*$_2$), 5.15 – 5.06 (m, 1H, Ar-N*H*), 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× -C*H*(Ad)), 2.00 (s, 2H, -C*H*$_2$CONH$_2$), 1.75 (quint, J = 7.3 Hz, 2H, H-10), 1.63 – 1.41 (m, 16H, 6× -C*H*$_2$(Ad) and 2× -C*H*$_2$, H-11 and H-15), 1.41 – 1.29 (m, 6H, 3× -C*H*$_2$, H-(12-14)). ^{13}C NMR (125 MHz, $CDCl_3$, 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 $[C_{30}H_{43}ClN_4O+H]^+$ 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; H_2O H-Bond – water hydrogen bond; Conv. H-Bond – conventional hydrogen bond; π – π-orbitals; HD – H-Donor; HA – H-Acceptor; + – positive; – – negative

Table S1. Scores for docked ligands.

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

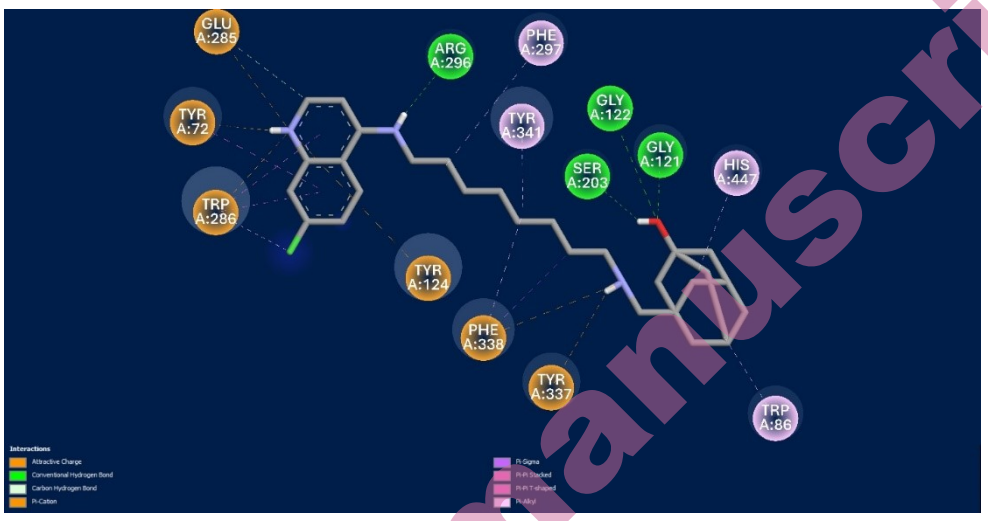


Figure S1. Map of interactions of compound **6** with AChE.

Table S2. 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

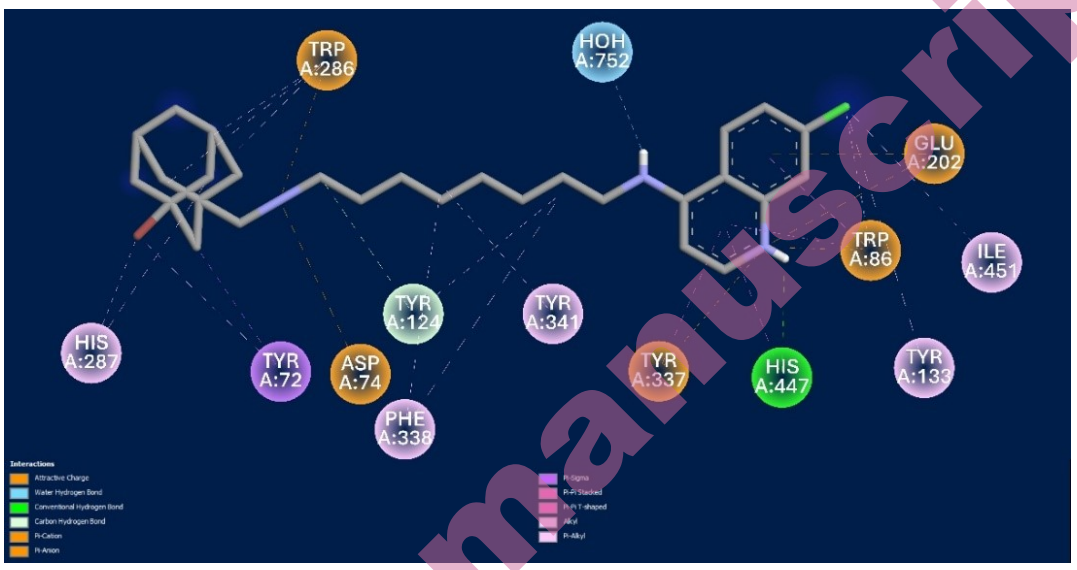


Figure S2. Map of interactions of compound **7** with AChE.

Table S3. 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_2O 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

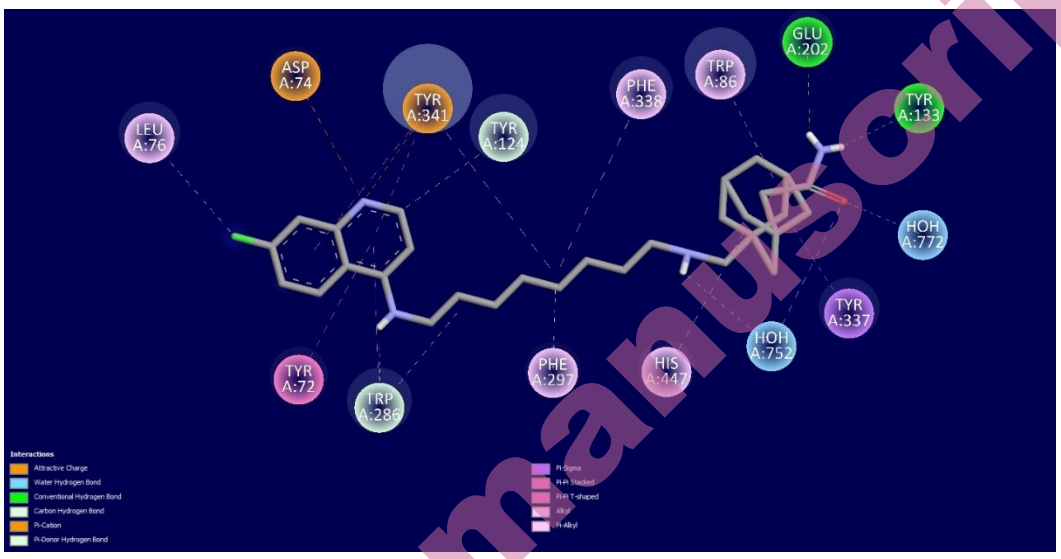


Figure S3. Map of interactions of compound **8** with AChE.

Table S4. 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_2O H-Bond;Conv. H-Bond	HOH752:H1, HD	8:O1, HA
HOH772:H1 - 8:O1	H-Bond	H_2O H-Bond;Conv. H-Bond	HOH772:H1, HD	8:O1, HA
8:H20 - HOH752:OH2	H-Bond	H_2O 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

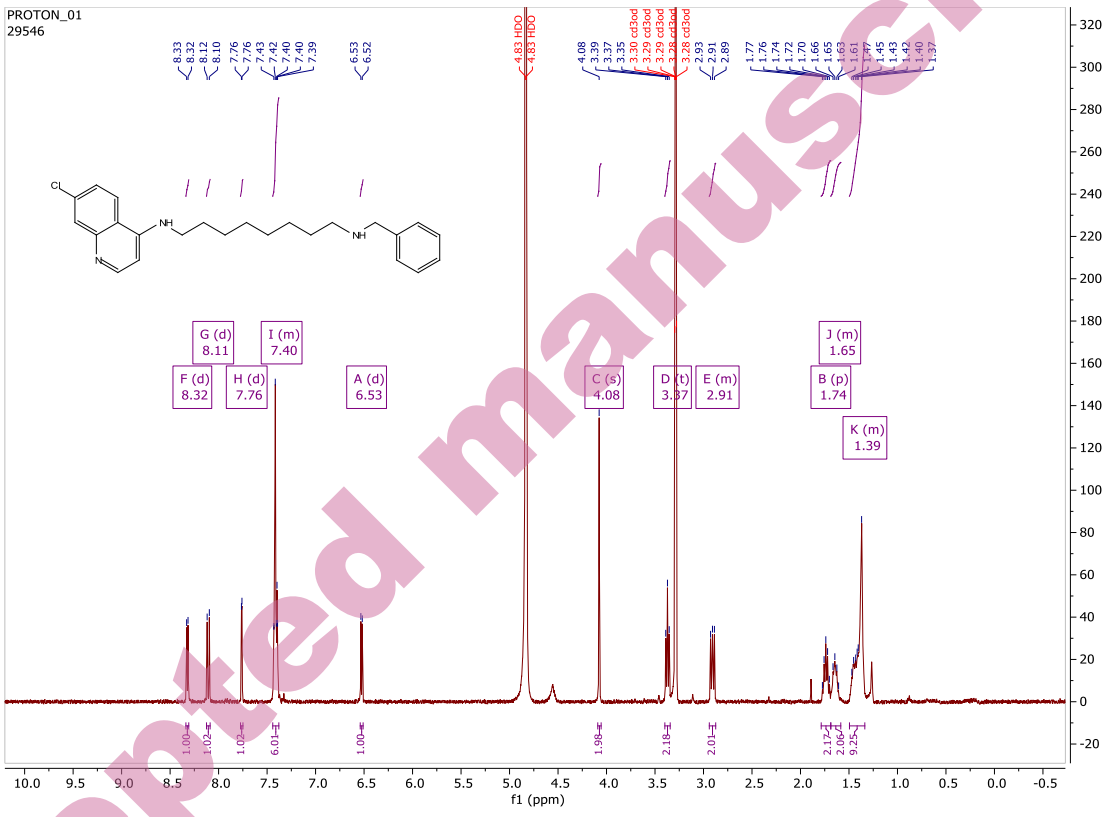
Table S5. In silico physicochemical properties of 4-AQ hybrids with adamantane.

Comp.	MW (g/mol)	RB	HBA	HBD	TPSA (Å²)	Log *P*	pK_{a1} [a]	pK_{a2} [a]	log*D* [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

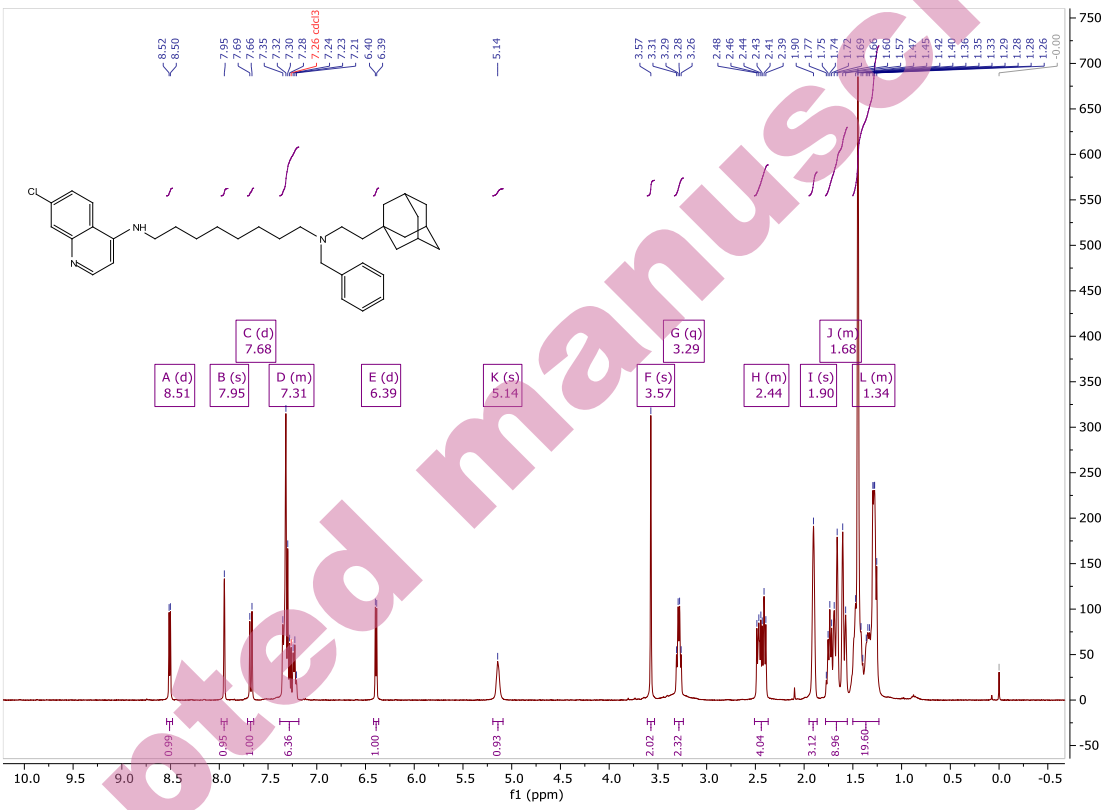
[a] pK_{a1} belongs to the quinoline ring, pK_{a2} belongs to the terminal basic amino group; [b] logD value at pH = 7.4; [c] CNS MPO data were generated following instruction published in reference T. T. Wager, X. Hou, P. R. Verhoest, A. Villalobos, *ACS Chem. Neurosci.*, **1** (2010) 435. https://doi.org/10.1021/cn100008c;

4. ^{1}H AND ^{13}C NMR SPECTRA

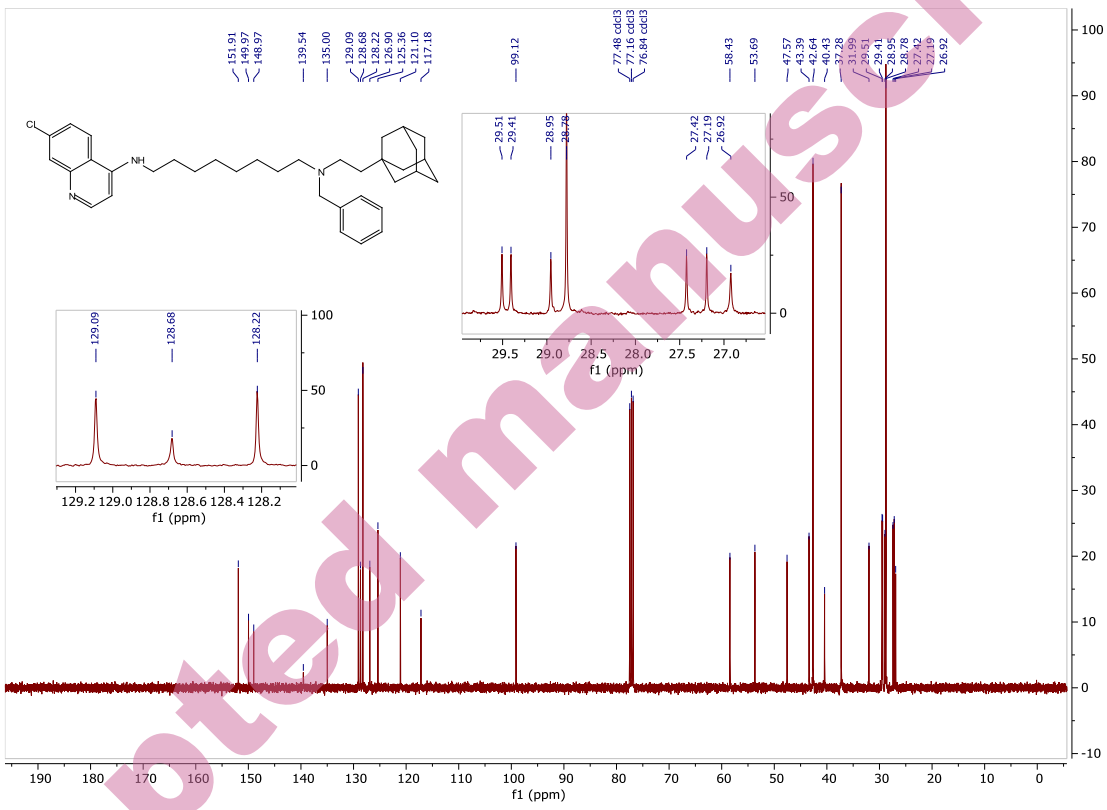
^{1}H NMR spectrum of N^{1}-benzyl-N^{8}-(7-chloroquinolin-4-yl)octane-1,8-diamine (2)



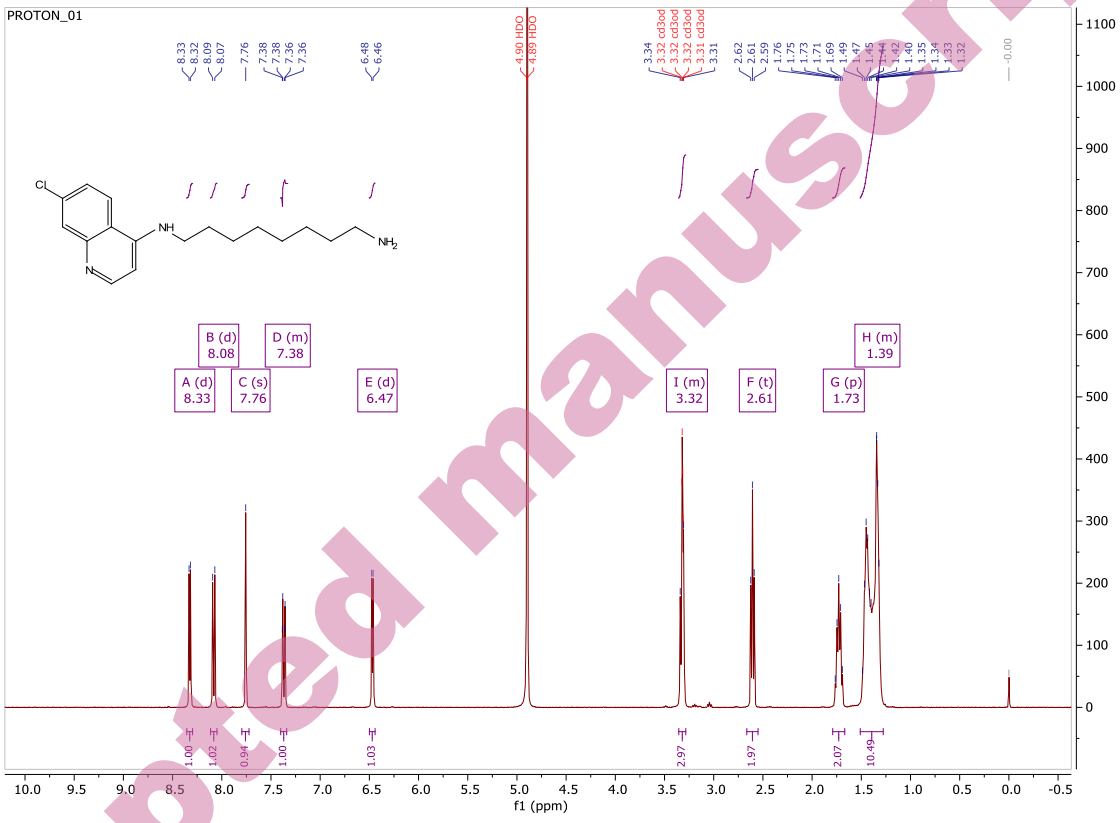
^{1}H NMR spectrum of N^{1}-(2-adamantan-1-yl)ethyl)-N^{1}-benzyl-N^{8}-(7-chloroquinolin-4-yl)octane-1,8-diamine (5)



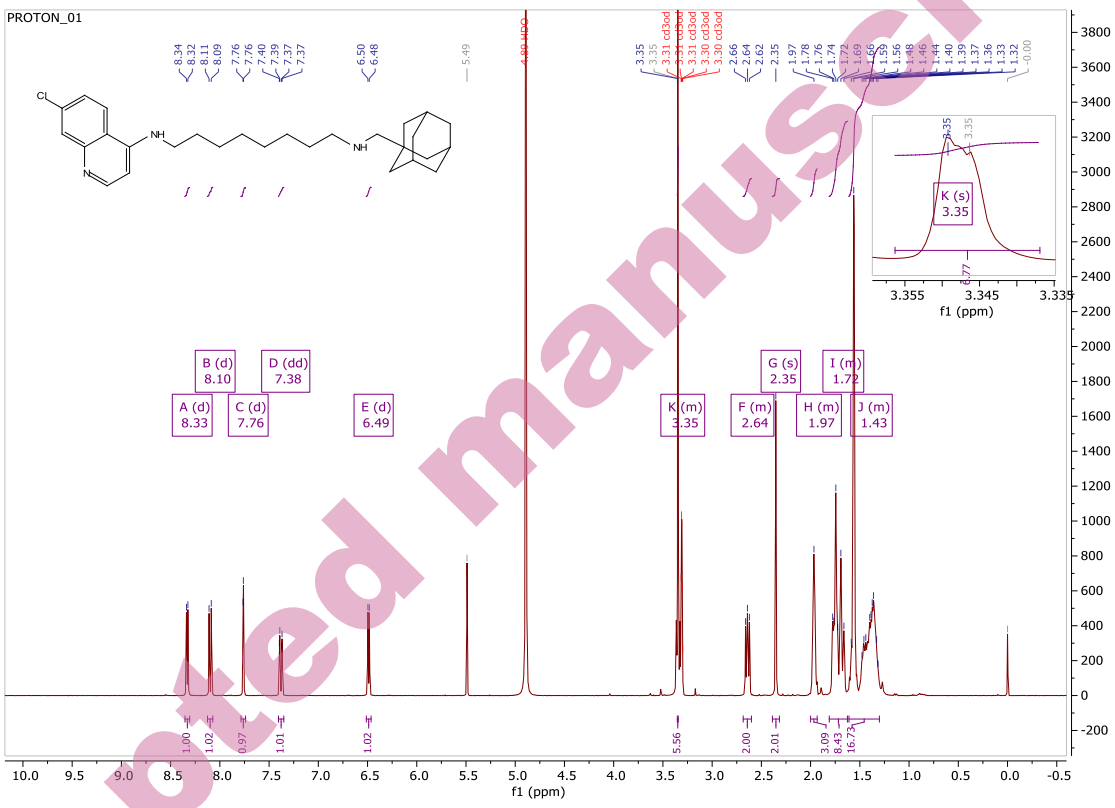
^{13}C NMR spectrum of N^1-(2-(adamantan-1-yl)ethyl)-N^1-benzyl-N^8-(7-chloroquinolin-4-yl)octane-1,8-diamine (5)



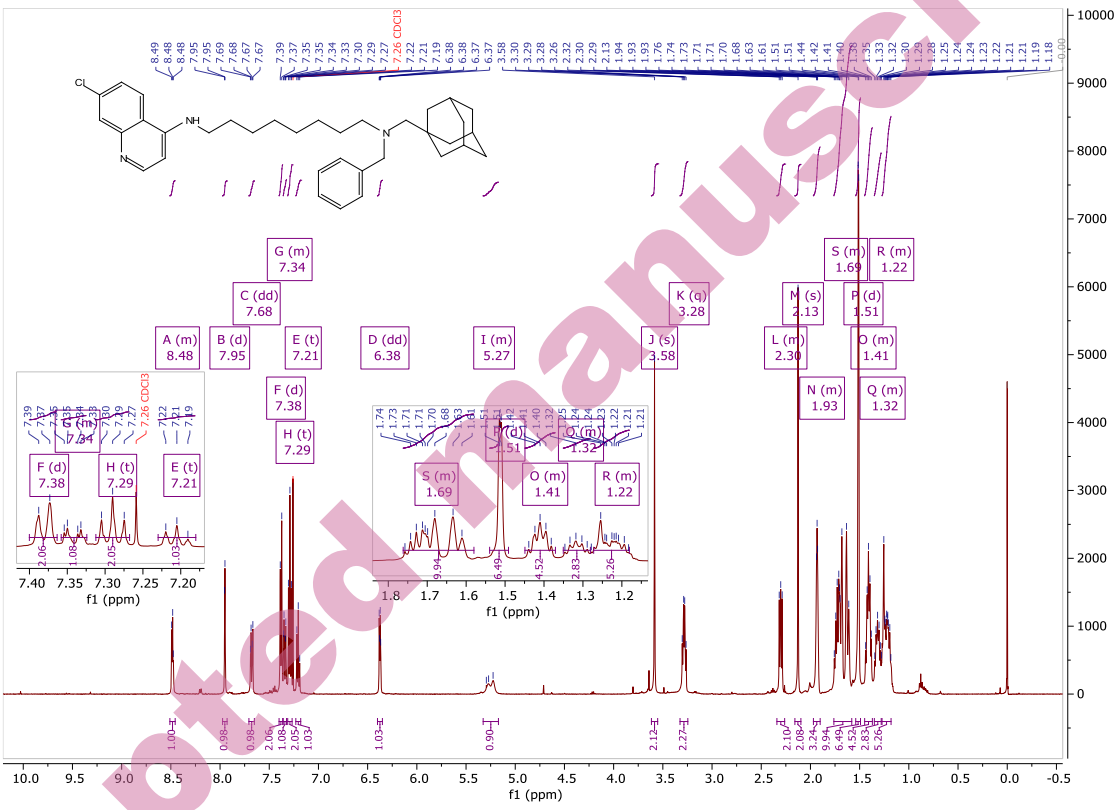
^{1}H NMR spectrum of N^1-(7-chloroquinolin-4-yl)octane-1,8-diamine (9)



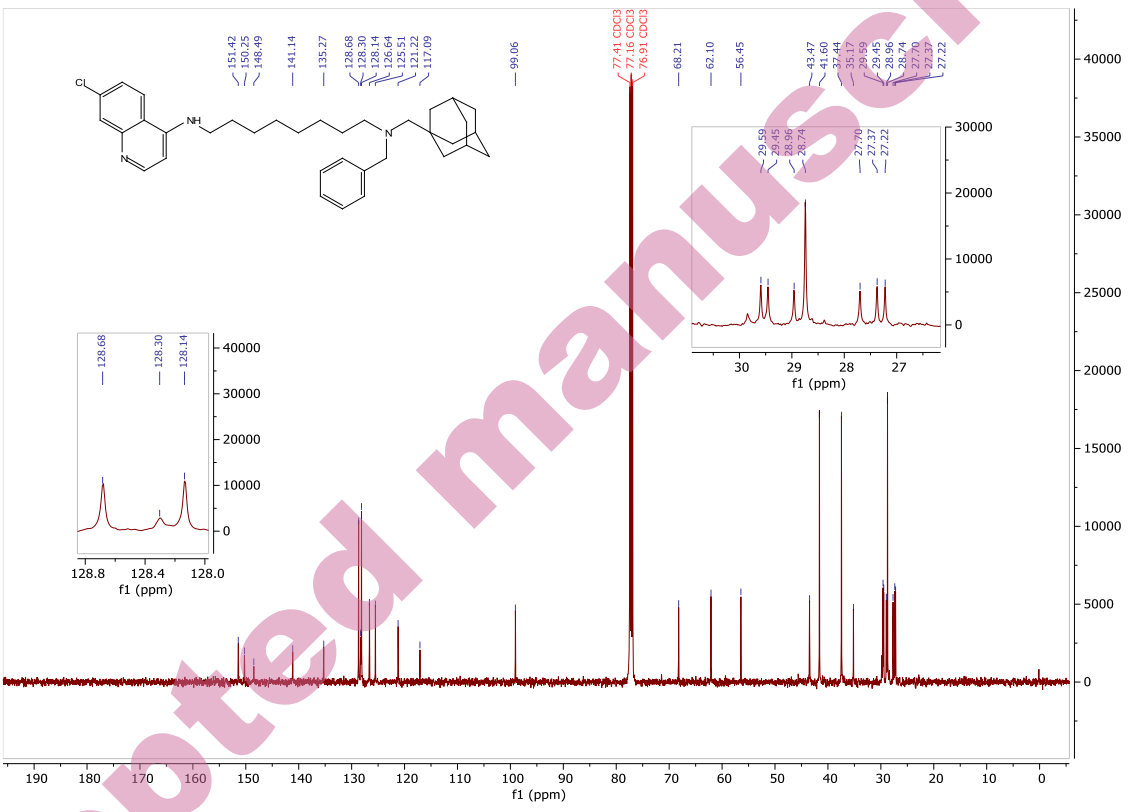
^{1}H NMR spectrum of N^{1}-((adamantan-1-yl)methyl)-N^{8}-(7-chloroquinolin-4-yl)octane-1,8-diamine (1)



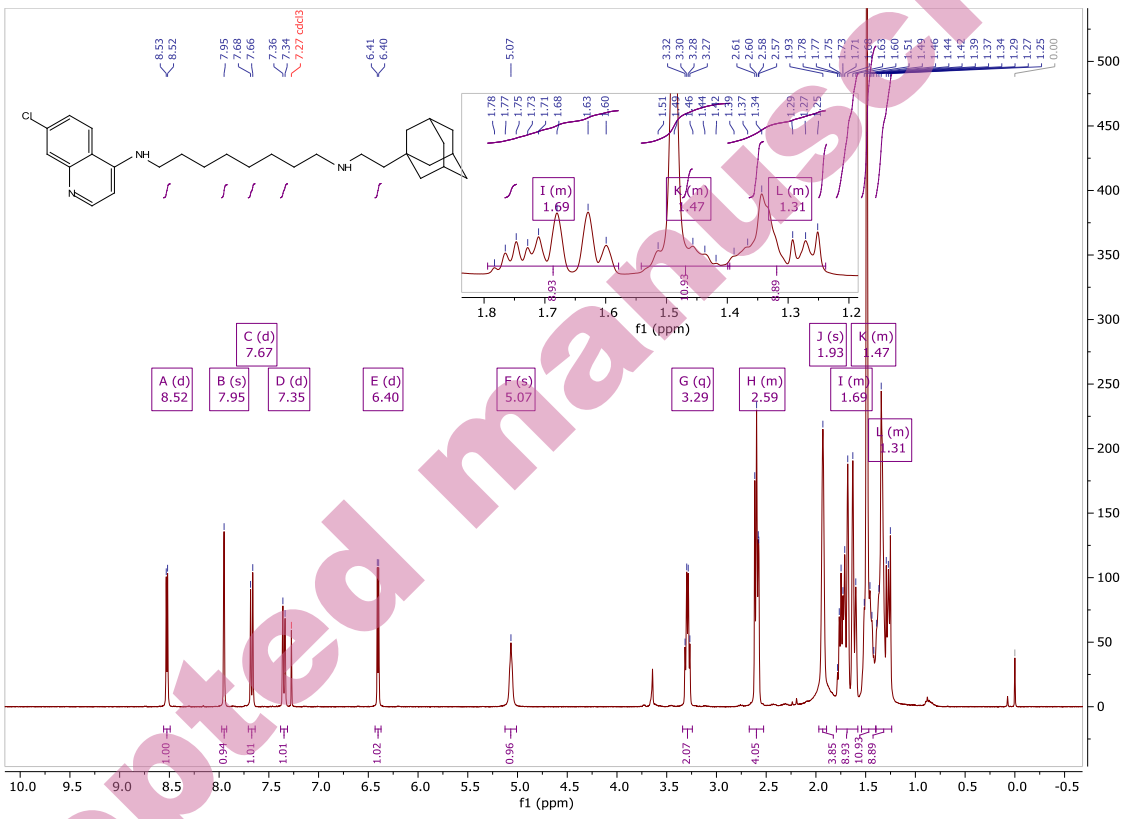
^{1}H NMR spectrum of N^1-((adamantan-1-yl)methyl)-N^1-benzyl-N^8-(7-chloroquinolin-4-yl)octane-1,8-diamine (4)



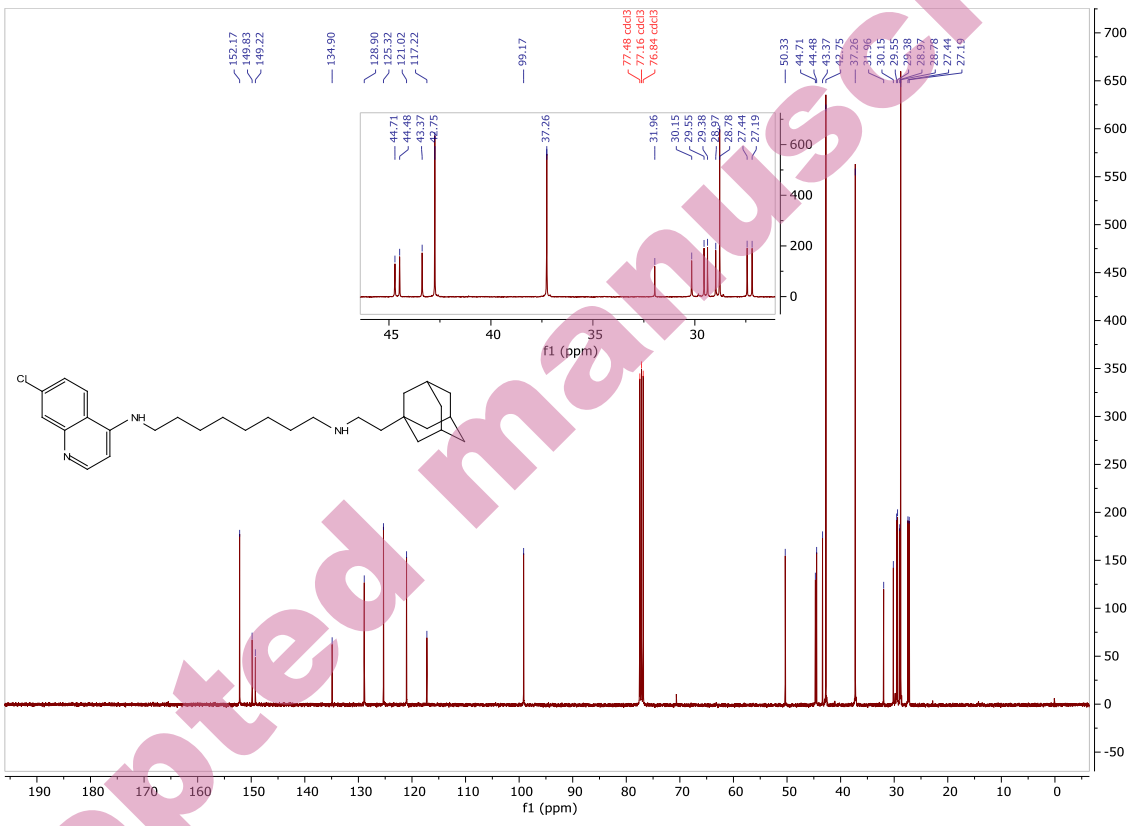
^{13}C NMR spectrum of N^1-((adamantan-1-yl)methyl)-N^1-benzyl-N^8-(7-chloroquinolin-4-yl)octane-1,8-diamine (4)



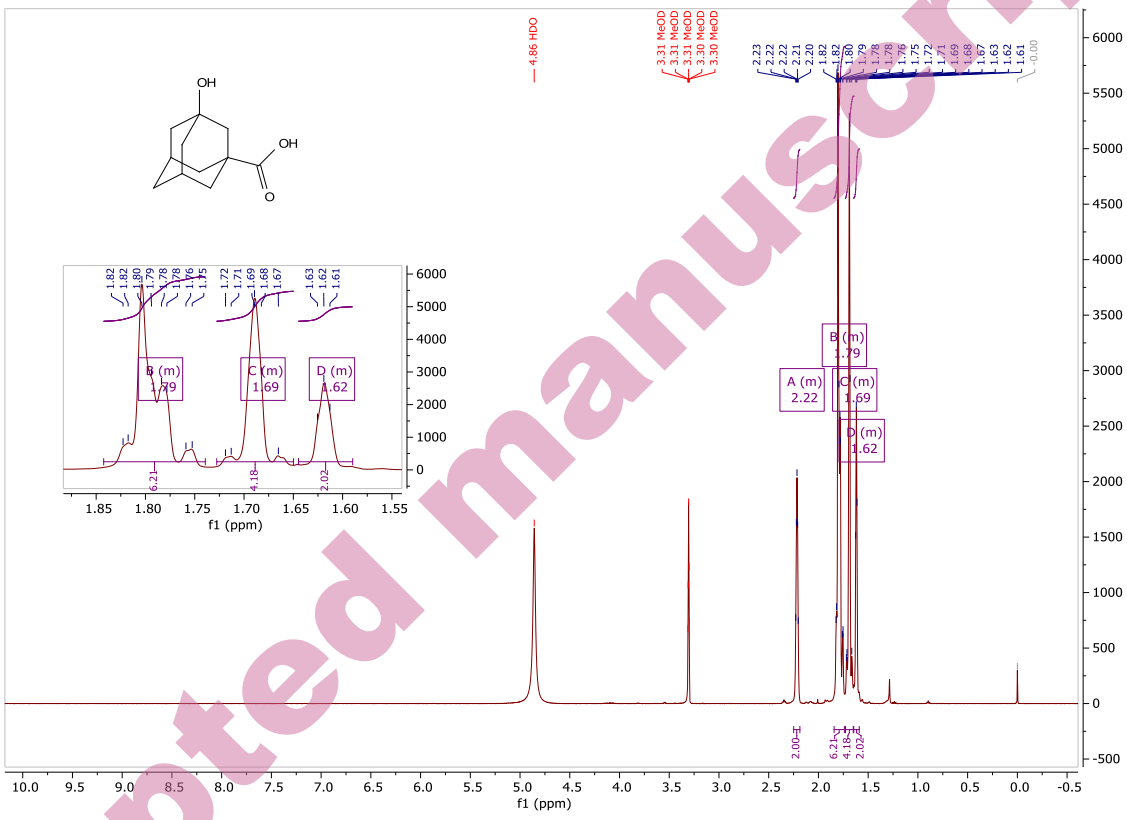
^{1}H NMR spectrum of N^1-(2-(adamantan-1-yl)ethyl)-N^8-(7-chloroquinolin-4-yl)octane-1,8-diamine (3)



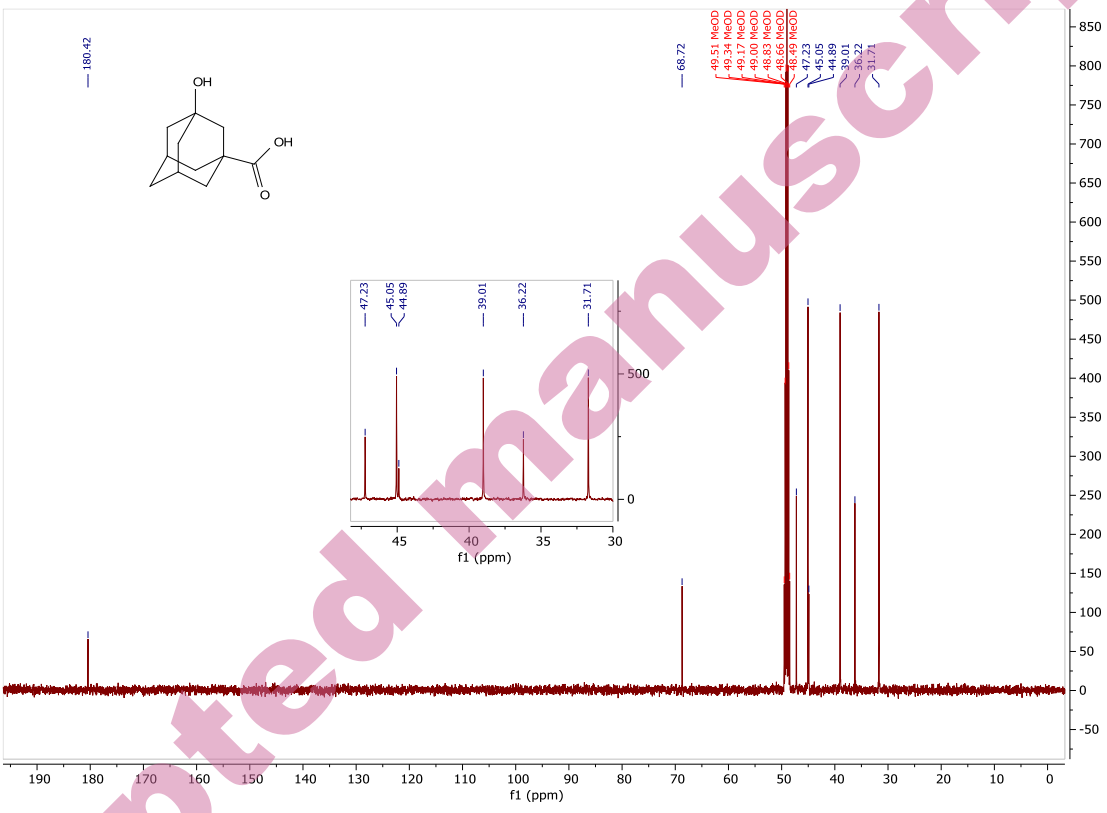
^{13}C NMR spectrum of N^1-(2-(adamantan-1-yl)ethyl)-N^8-(7-chloroquinolin-4-yl)octane-1,8-diamine (3)



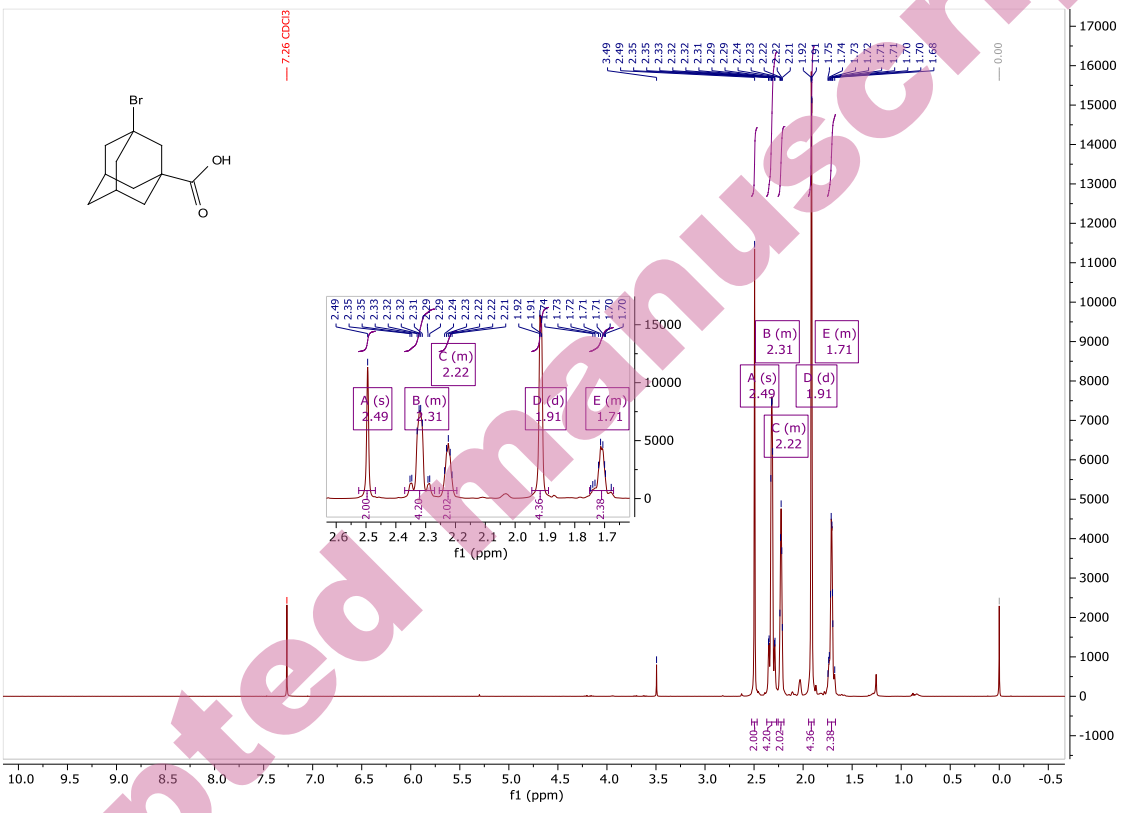
^{1}H NMR spectrum of 3-hydroxyadamantane-1-carboxylic acid (11)



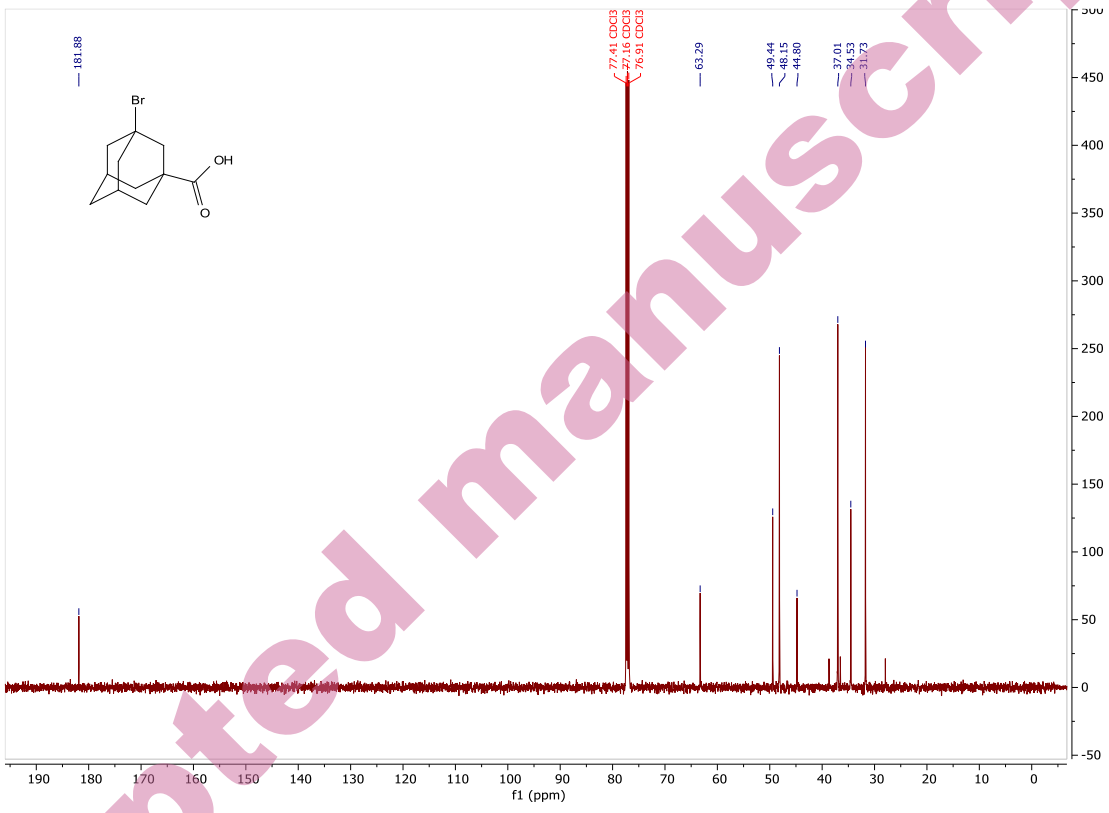
^{13}C NMR spectrum of 3-hydroxyadamantane-1-carboxylic acid (11)



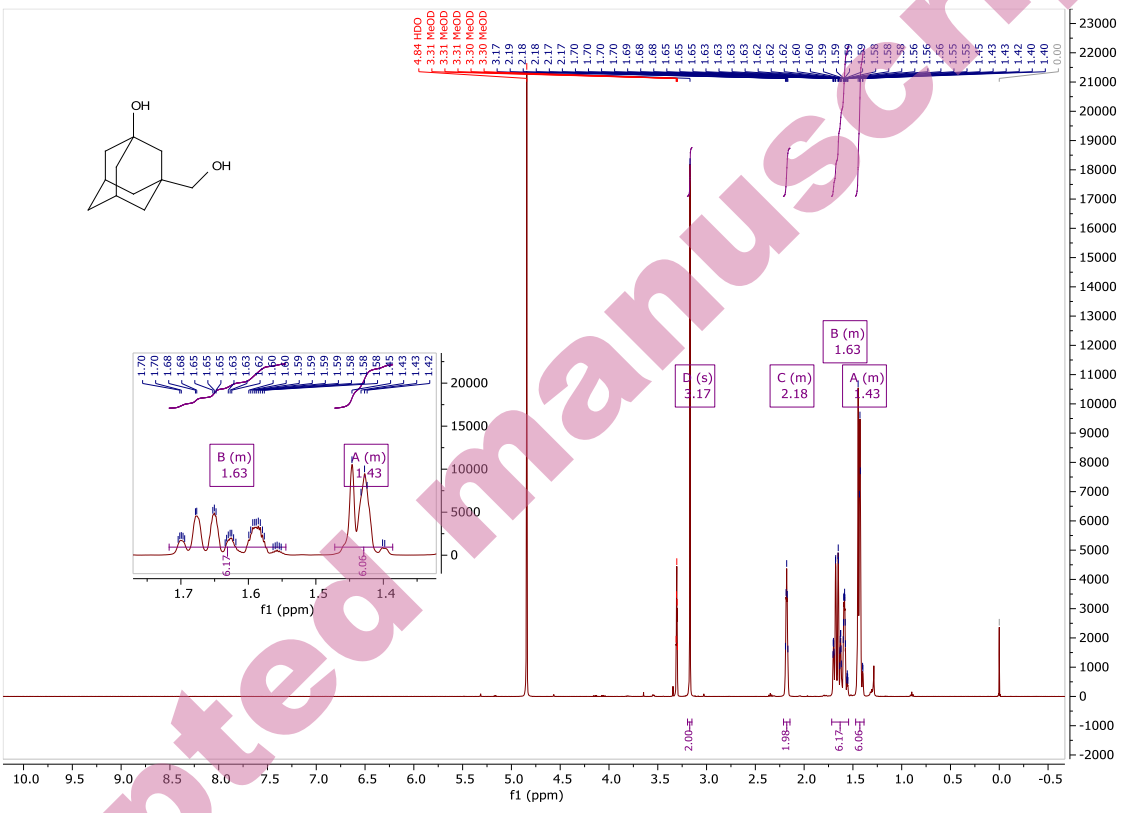
^{1}H NMR spectrum of 3-bromoadamantane-1-carboxylic acid (12)



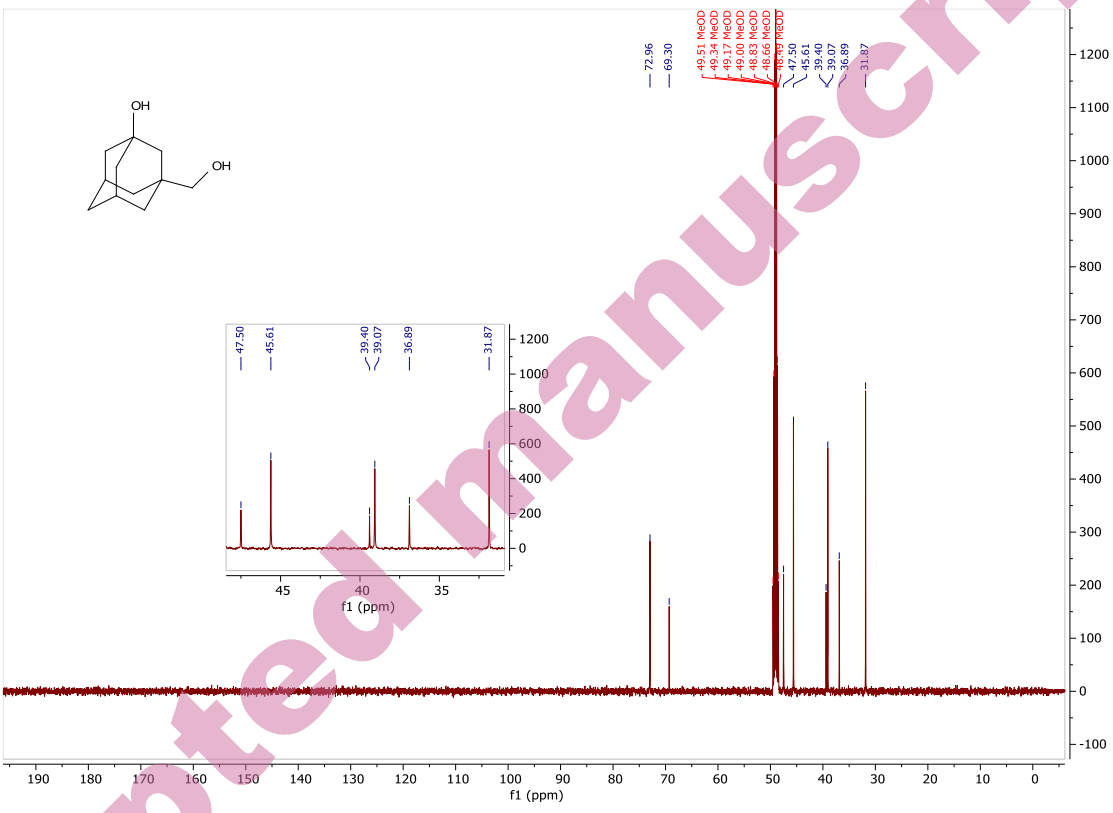
^{13}C NMR spectrum of 3-bromoadamantane-1-carboxylic acid (12)



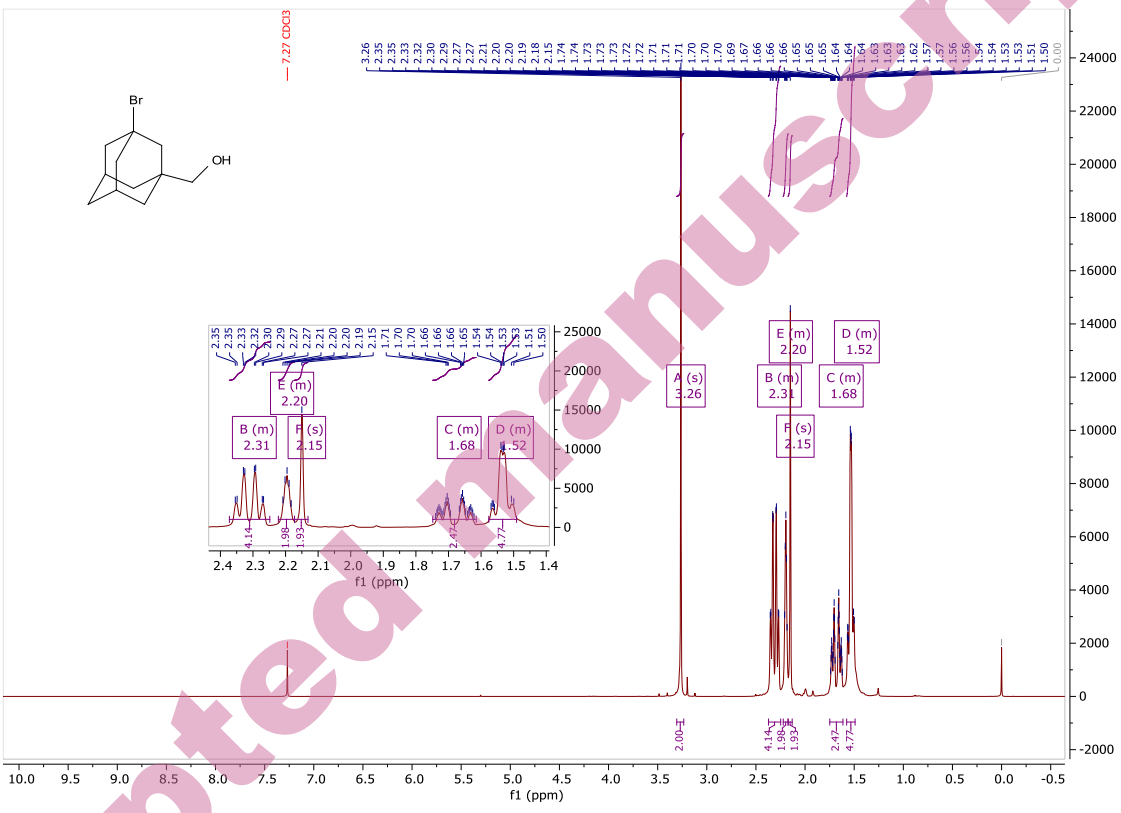
^{1}H NMR spectrum of 3-(hydroxymethyl)adamantan-1-ol (13)



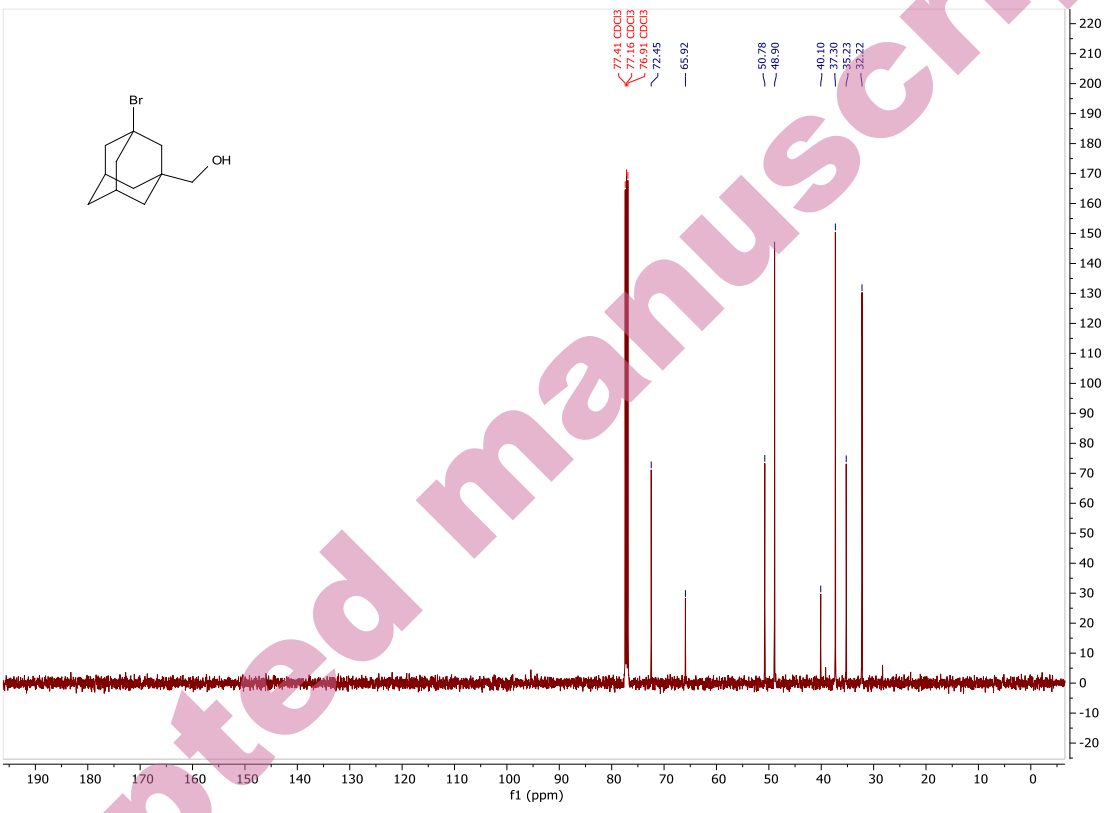
^{13}C NMR spectrum of 3-(hydroxymethyl)adamantan-1-ol (13)



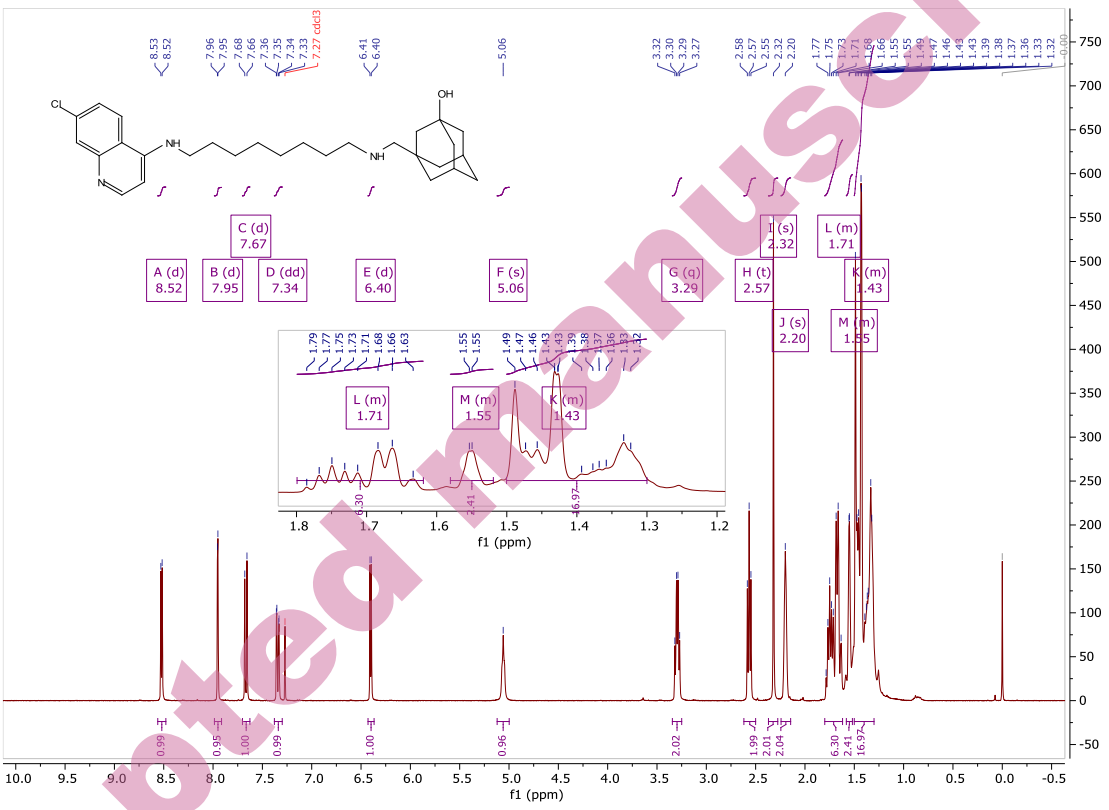
^{1}H NMR spectrum of (3-bromoadamantan-1-yl)methanol (14)



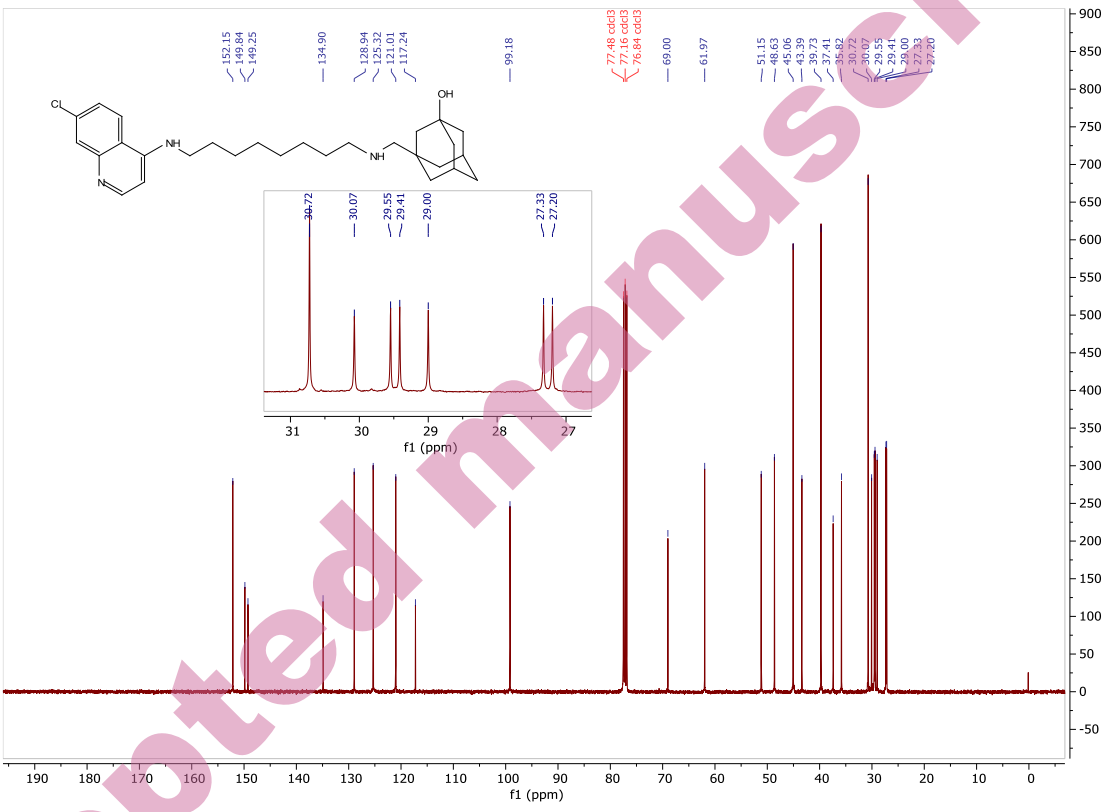
^{13}C NMR spectrum of (3-bromoadamantan-1-yl)methanol (14)



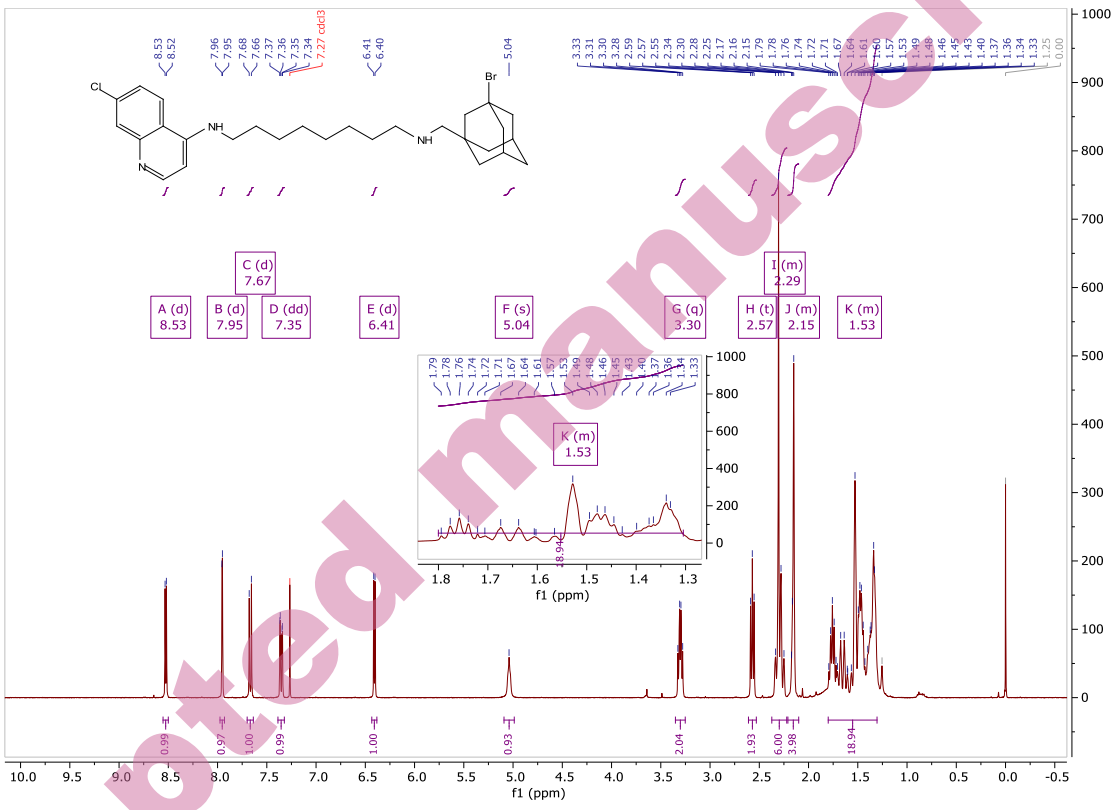
^{1}H NMR spectrum of 3-(((8-((7-chloroquinolin-4-yl)amino)octyl)amino)methyl)adamantan-1-ol (6)



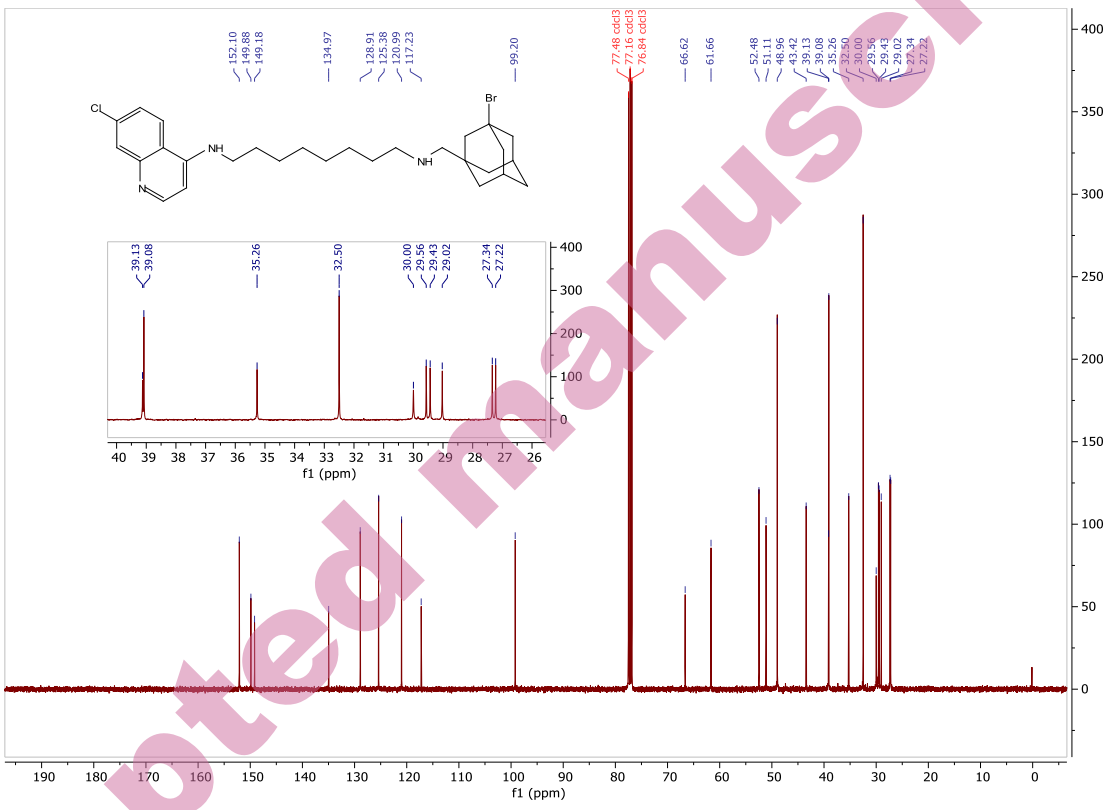
^{13}C NMR spectrum of 3-(((8-((7-chloroquinolin-4-yl)amino)octyl)amino)methyl)adamantan-1-ol (6)



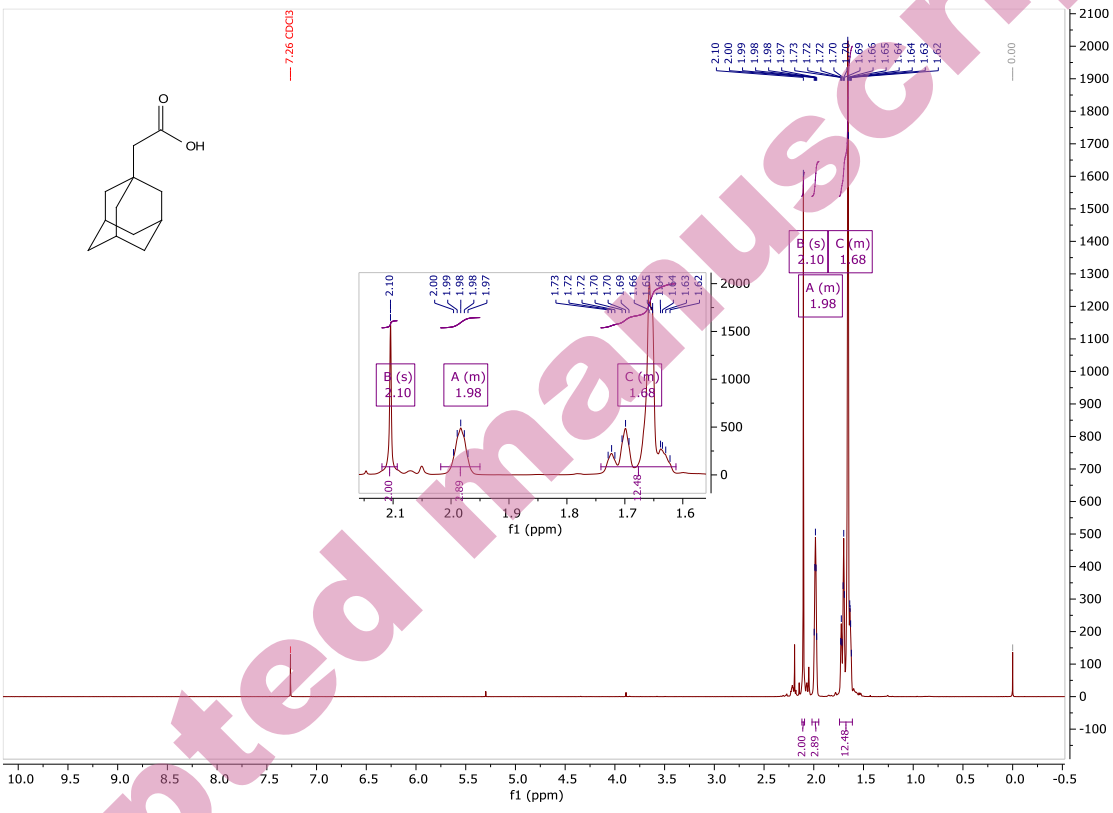
^{1}H NMR spectrum of N^{1}-((3-bromoadamantan-1-yl)methyl)-N^{8}-(7-chloroquinolin-4-yl)octane-1,8-diamine (7)



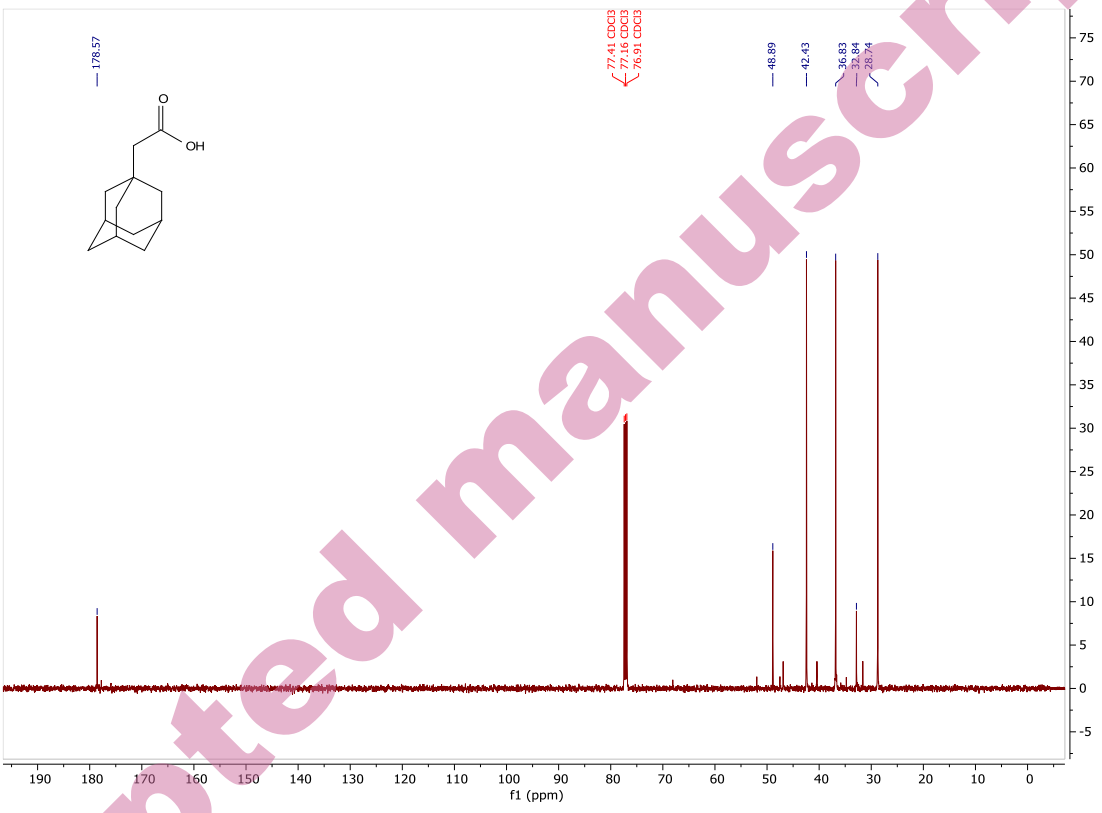
^{13}C NMR spectrum of N^1-((3-bromoadamantan-1-yl)methyl)-N^8-(7-chloroquinolin-4-yl)octane-1,8-diamine (7)



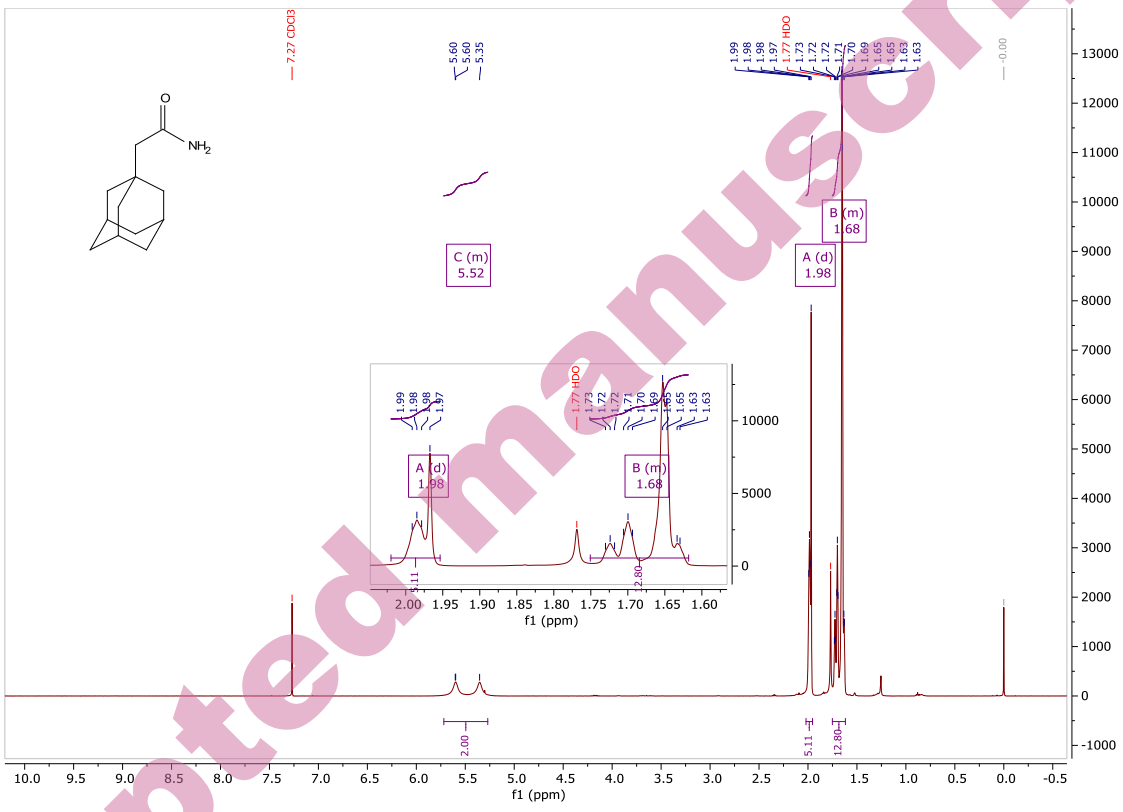
^{1}H NMR spectrum of 1-adamantaneacetic acid (18)



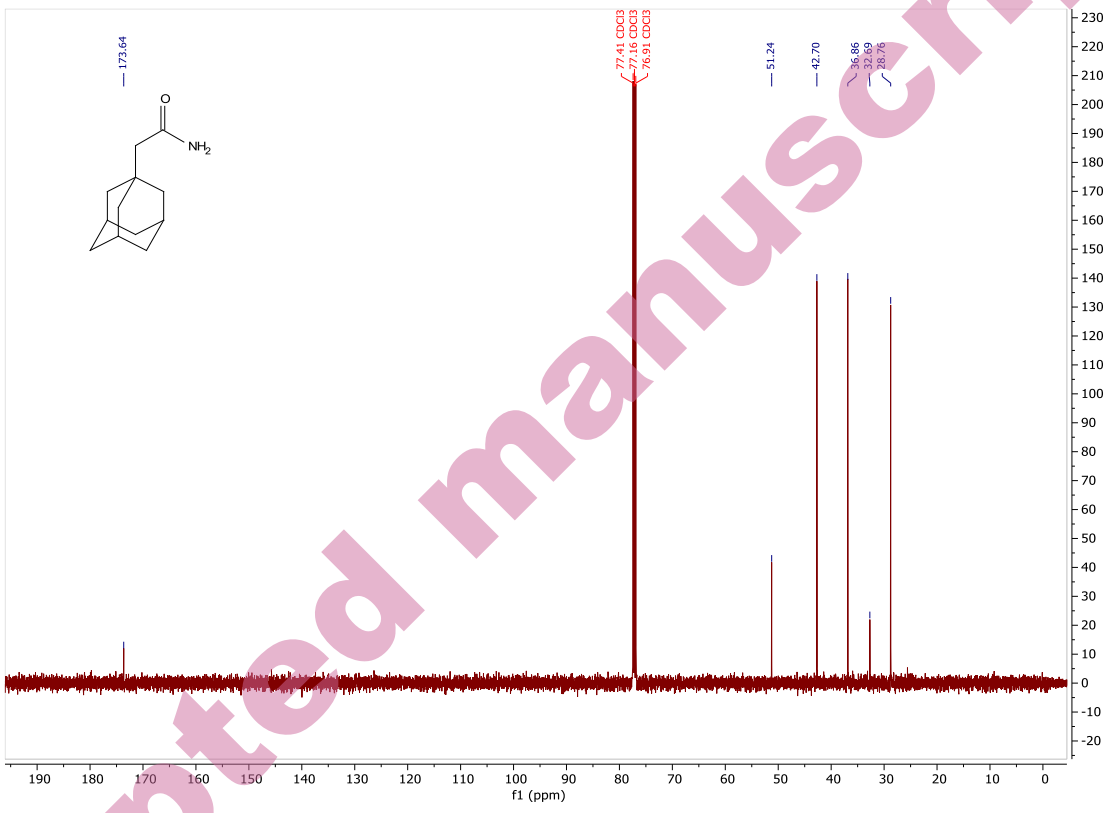
^{13}C NMR spectrum of 1-adamantaneacetic acid (18)



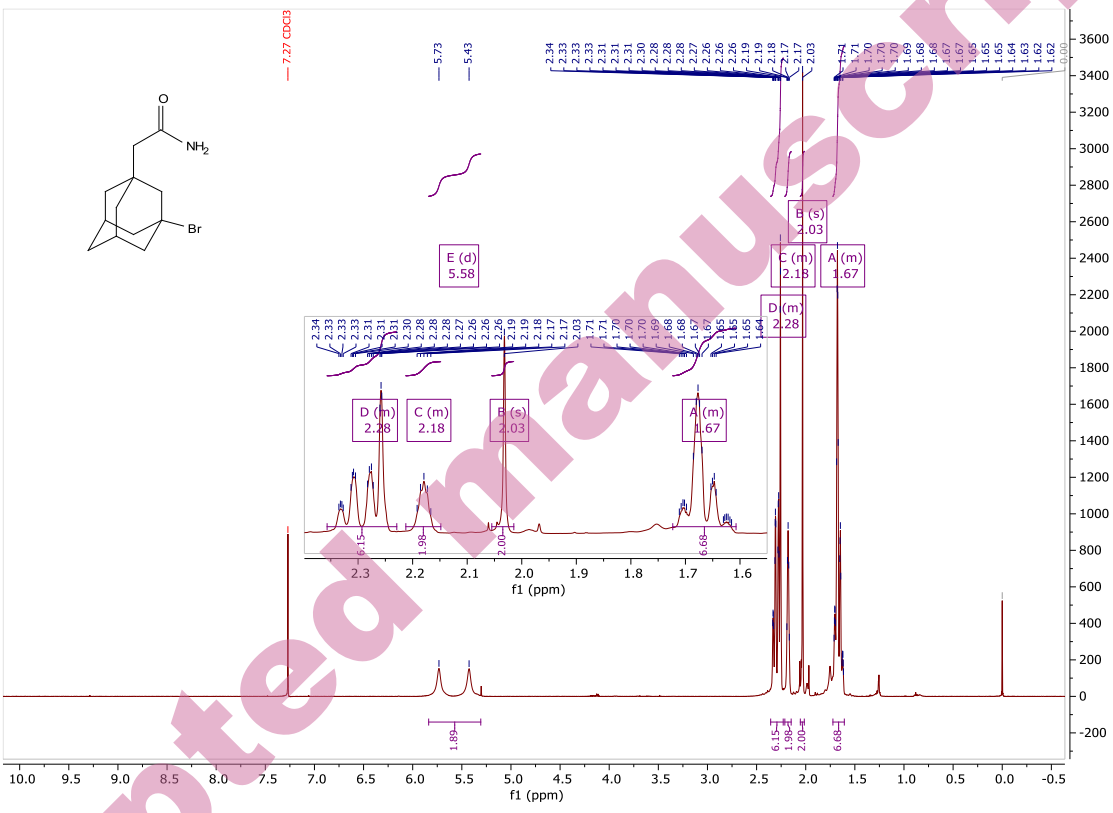
^{1}H NMR spectrum of 1-adamantaneacetamide (19)



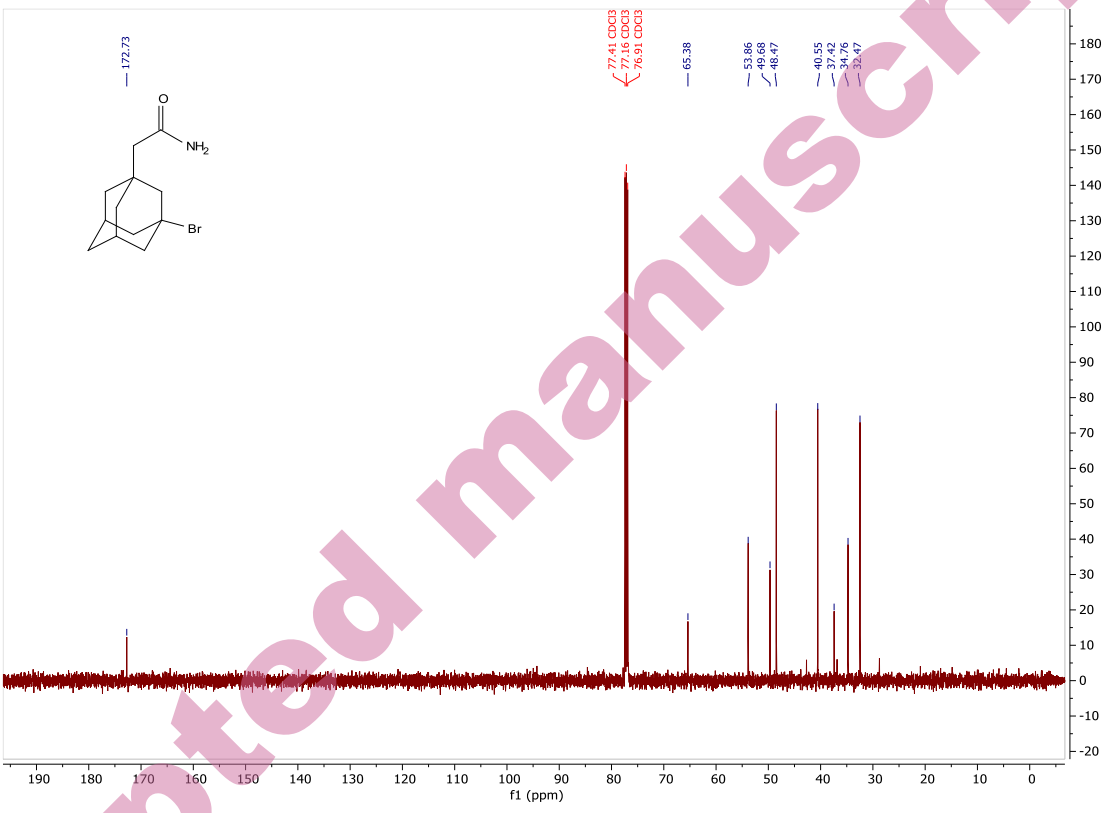
^{13}C NMR spectrum of 1-adamantaneacetamide (19)



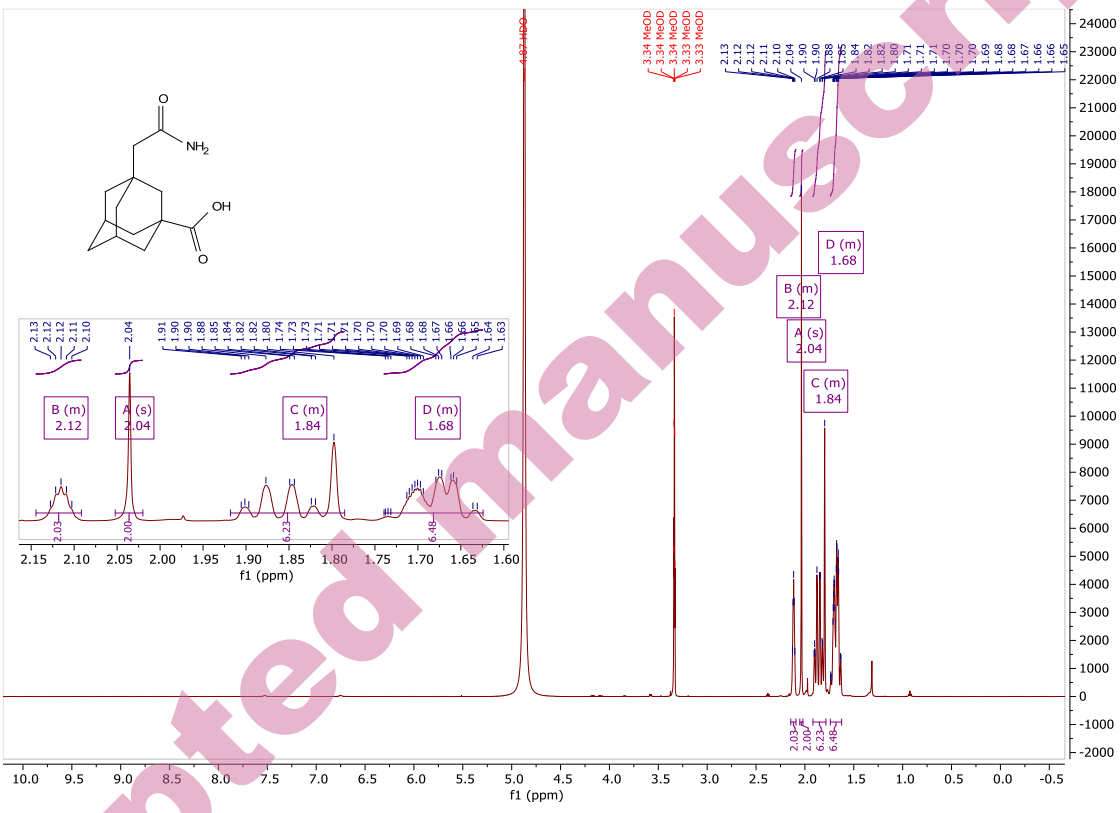
^{1}H NMR spectrum of 3-bromo-(1-adamantaneacetamide) (20)



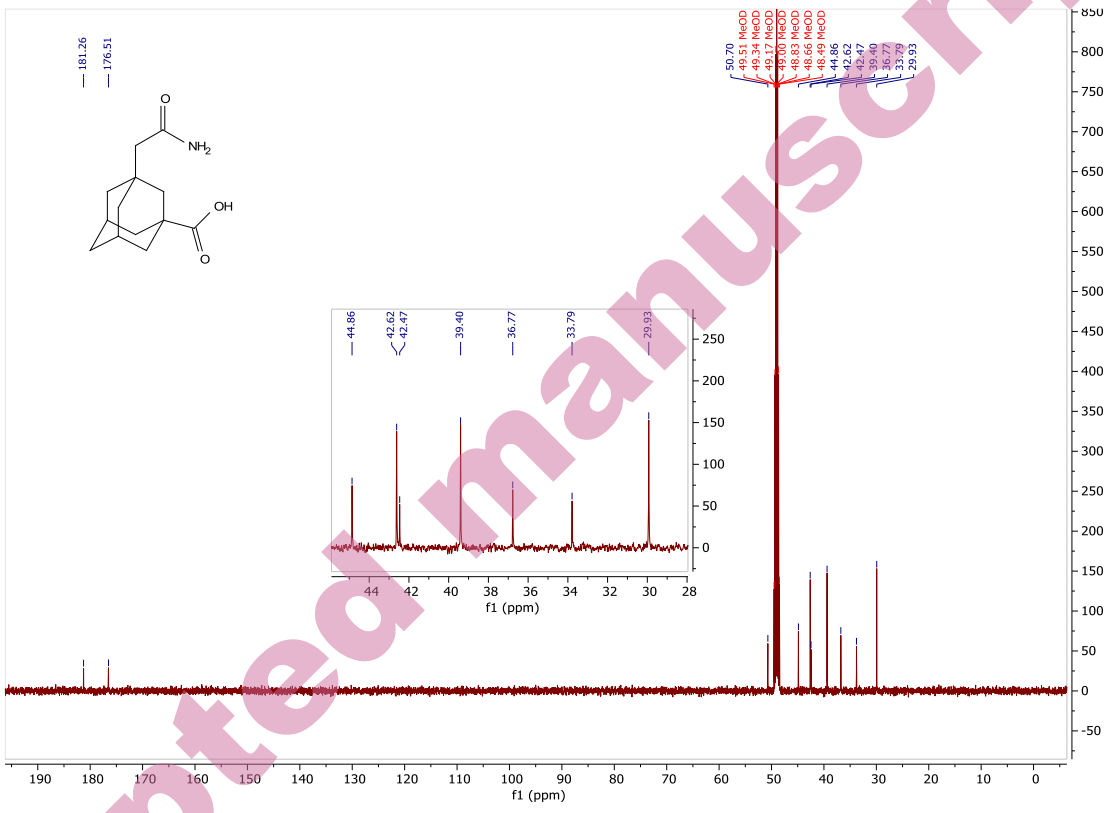
^{13}C NMR spectrum of 3-bromo-(1-adamantaneacetamide) (20)



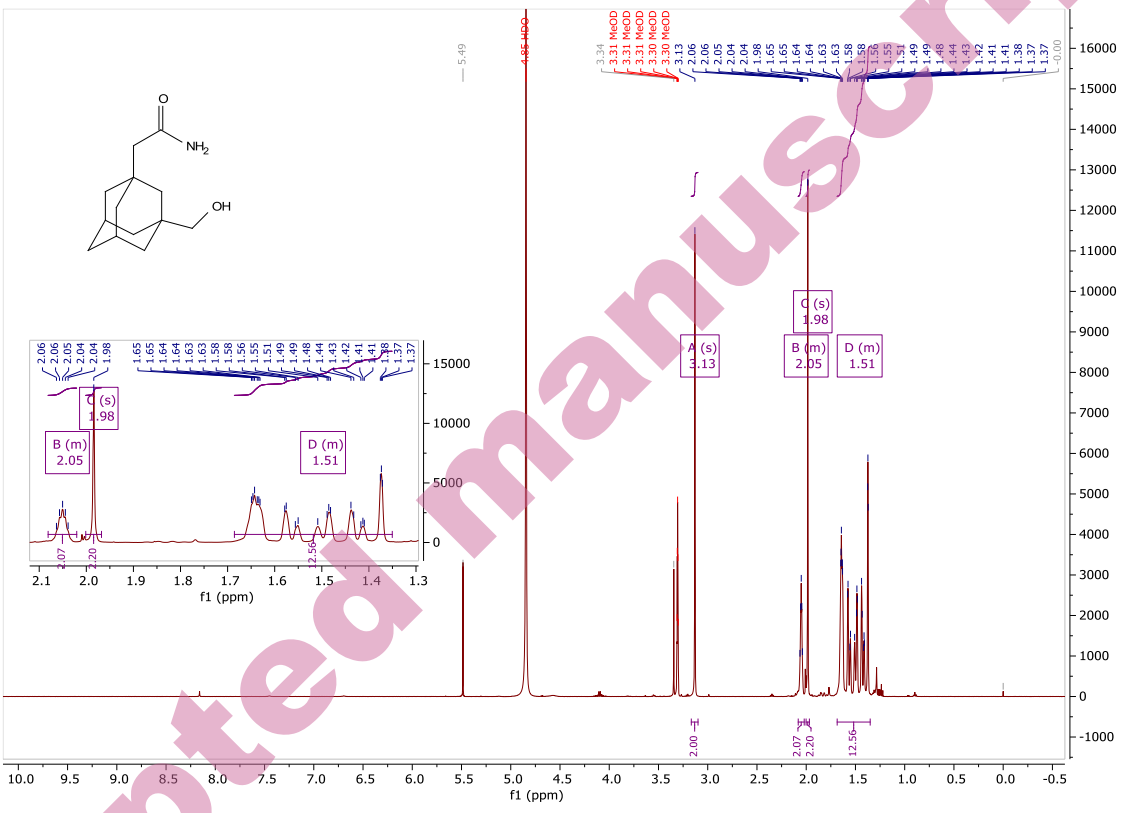
^{1}H NMR spectrum of 3-(2-amino-2-oxoethyl)adamantane-1-carboxylic acid (21)



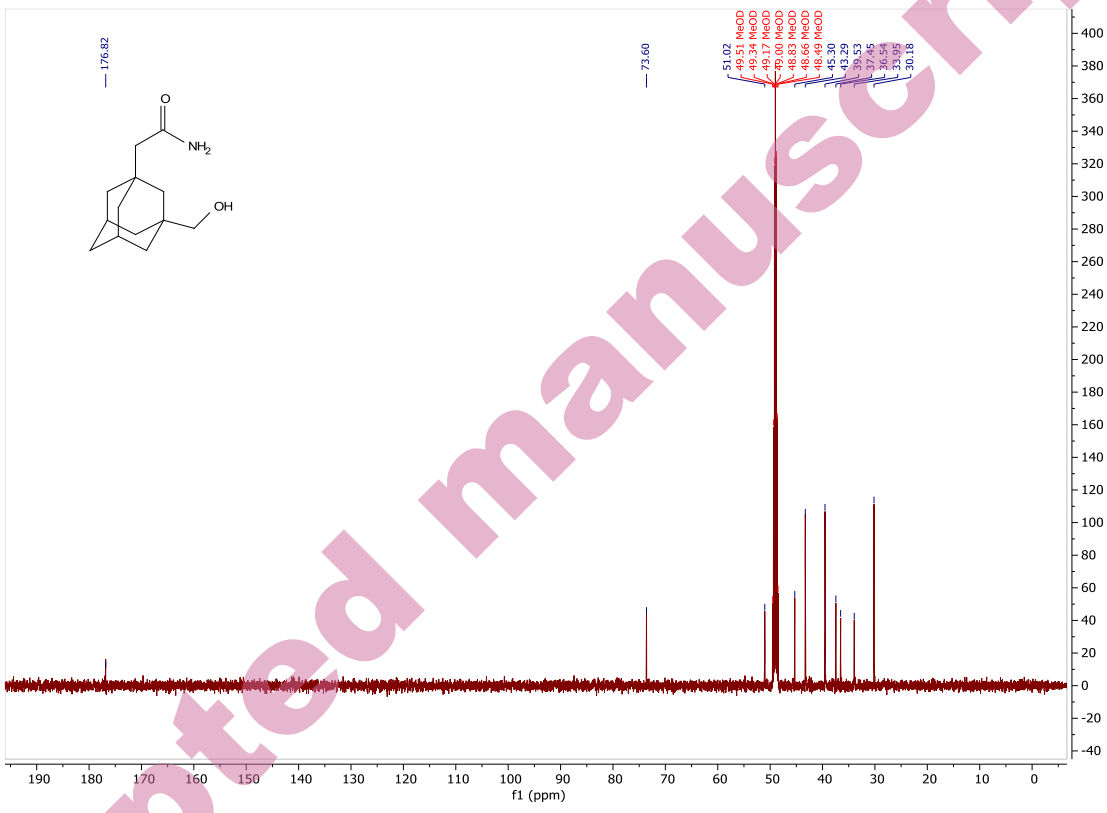
^{13}C NMR spectrum of 3-(2-amino-2-oxoethyl)adamantane-1-carboxylic acid (21)



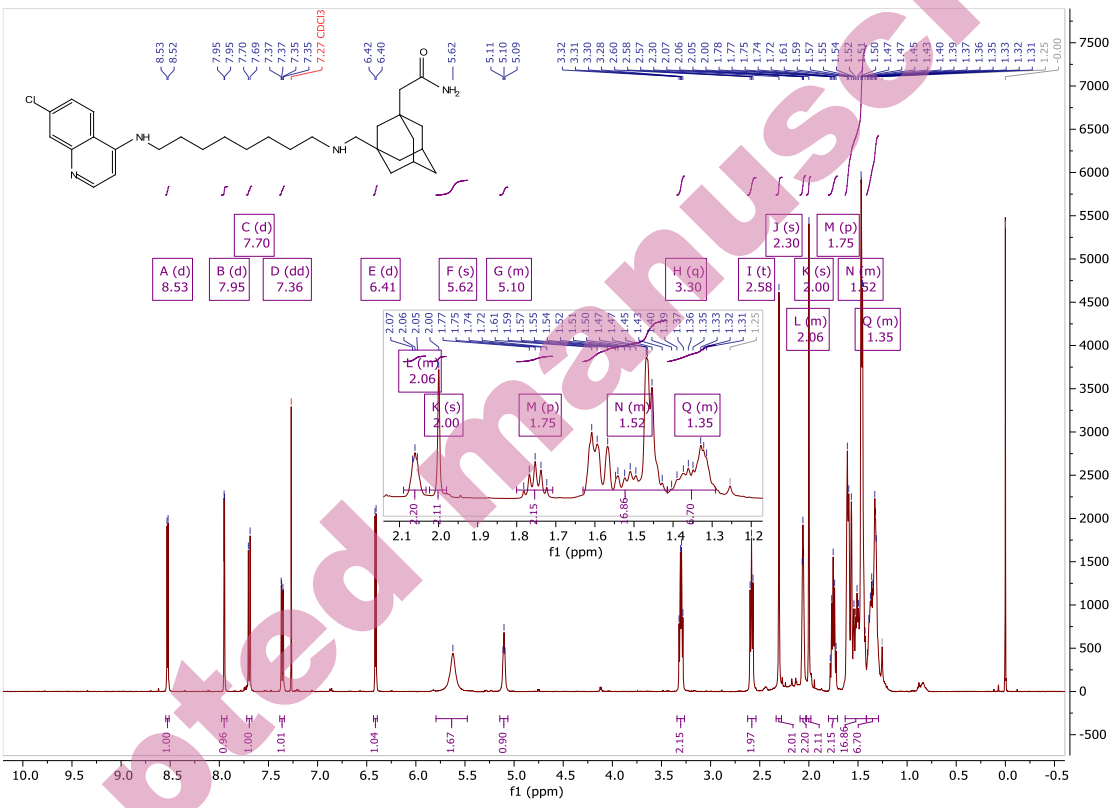
^{1}H NMR spectrum of 2-(3-(hydroxymethyl)adamantan-1-yl)acetamide (22)



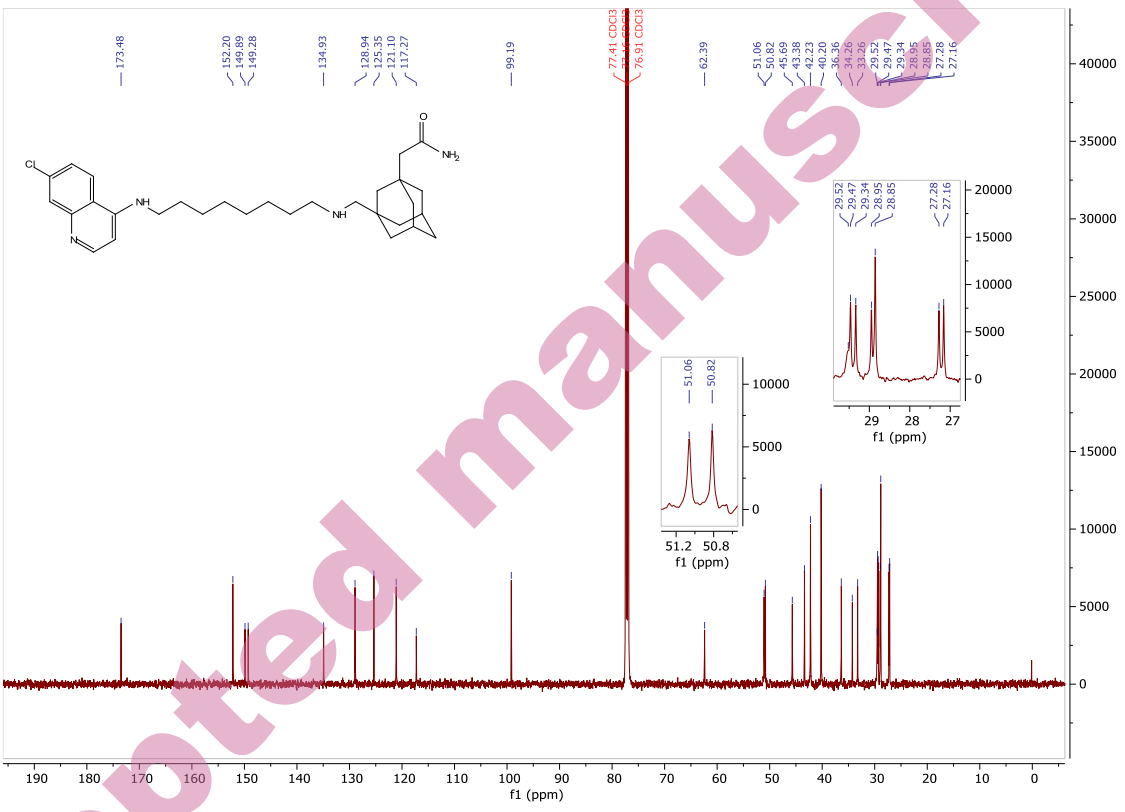
^{13}C NMR spectrum of 2-(3-(hydroxymethyl)adamantan-1-yl)acetamide (22)



^{1}H NMR spectrum of 2-(3-(((8-((7-chloroquinolin-4-yl)amino)octyl)amino)methyl)adamantan-1-yl)acetamide (8)



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



5. HPLC PURITY CHROMATOGRAMS

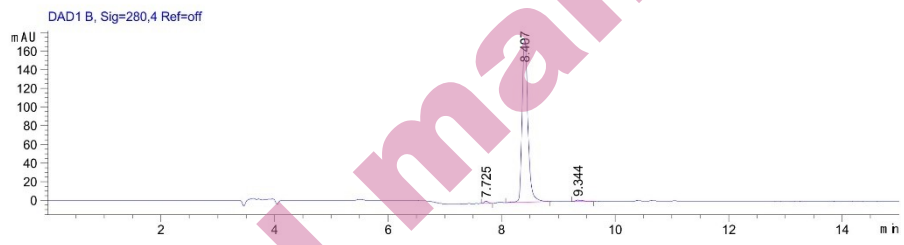
HPLC chromatogram of compound 3, method I

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.ACN.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 ***

HPLC chromatogram of compound 3, method II

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
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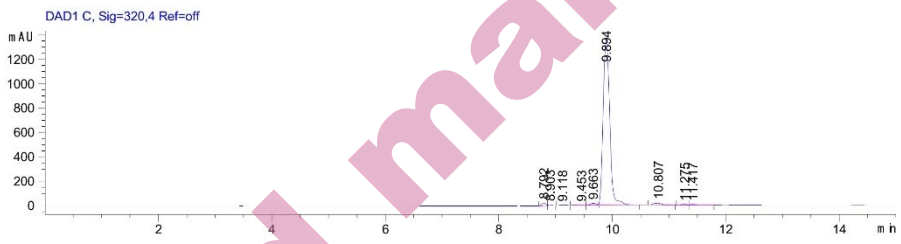


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                        Area Percent Report
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Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs
 Signal 3: DAD1 C, Sig=320,4 Ref=off

 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 BV 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 BV    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

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                        *** End of Report ***
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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.ACN.M (Sequence Method)
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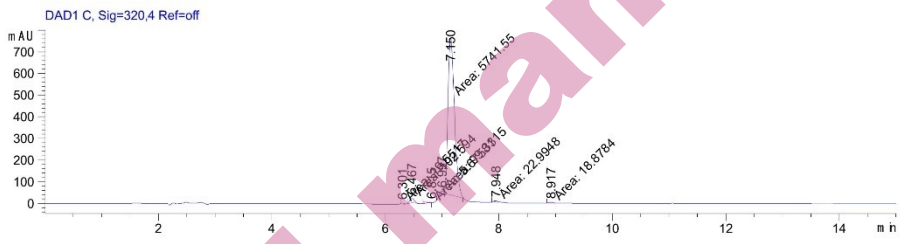


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                          Area Percent Report
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Sorted By             :      Signal
Multiplier            :      1.0000
Dilution              :      1.0000
Use Multiplier & Dilution Factor with ISTDs

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

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

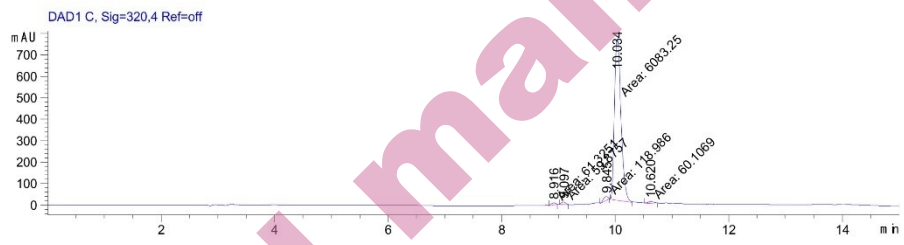
HPLC chromatogram of compound 4, method IV

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
```

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                          Area Percent Report
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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 Type  Width     Area      Height      Area
  #   [min]        [min]   [mAU*s]     [mAU]        %
----|-------|----|-------|----------|----------|-------|
  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 ***
```
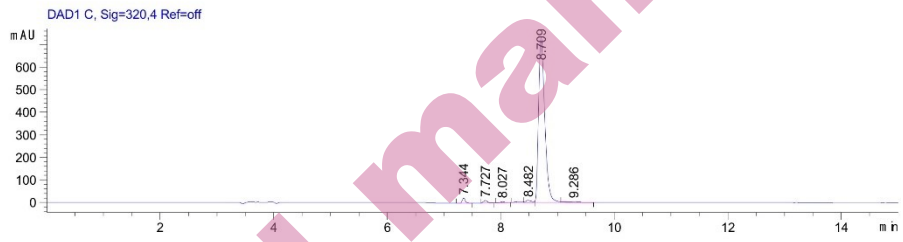

HPLC chromatogram of compound 5, method I

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.ACN.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 ***
```

HPLC chromatogram of compound 5, method II

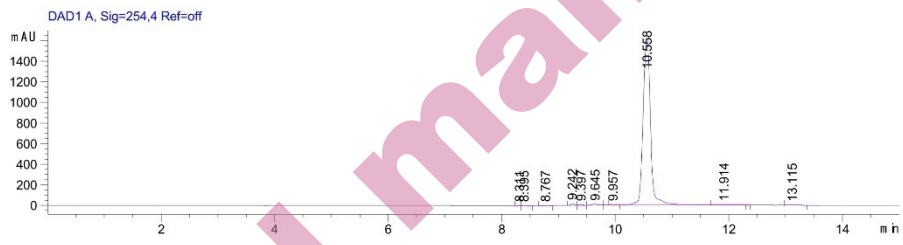
Sample Name: KBK48 Methoda II Compound **5**

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



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

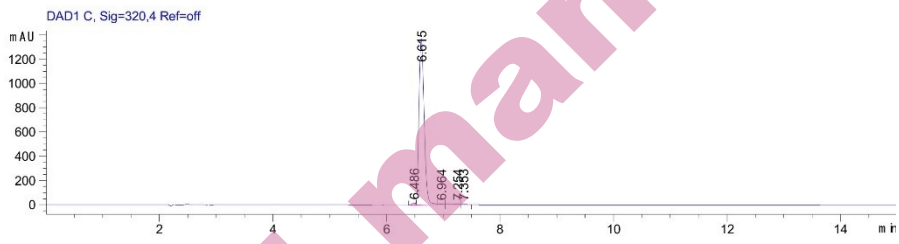
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.311	BV	0.0524	5.83001	1.77242	0.0388
2	8.395	VB	0.0748	25.67034	5.08937	0.1706
3	8.767	BB	0.0746	14.68180	2.92145	0.0976
4	9.242	BV	0.0710	86.24202	18.30317	0.5733
5	9.397	VB	0.0727	42.73519	9.10699	0.2841
6	9.645	BB	0.0963	66.82705	9.95200	0.4442
7	9.957	BV E	0.0935	13.95853	2.41147	0.0928
8	10.558	VV R	0.1402	1.47068e4	1615.26794	97.7614
9	11.914	VB 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.ACN.M (Sequence Method)
```

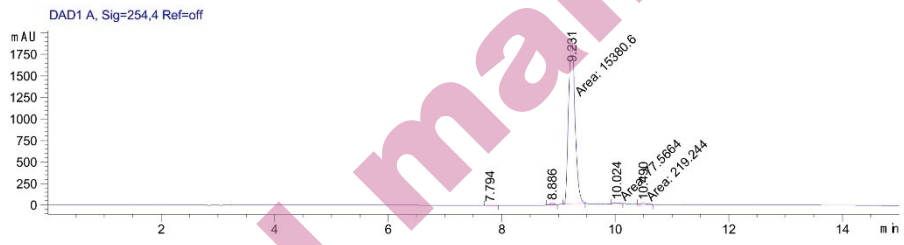



```
=========================================================================================
                              Fraction Information
=========================================================================================
No Fractions found.
=========================================================================================
=========================================================================================

=====================================================================
                          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 Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   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
```



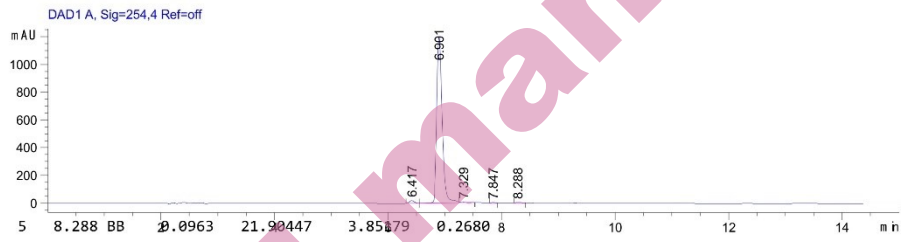

```
================================================================================
                          Fraction Information
================================================================================
No Fractions found.
================================================================================
================================================================================


======================================================================
                       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 Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   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

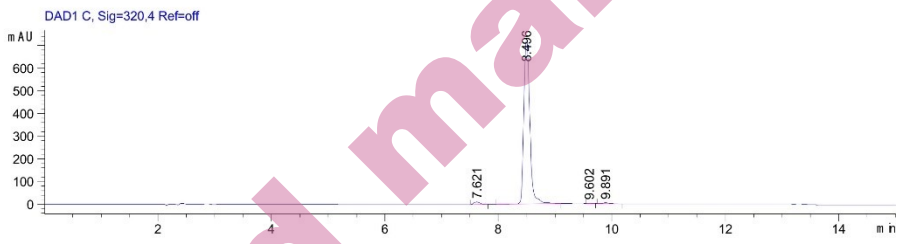
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	6.417	BV	0.0911	120.12967	20.90011	1.4696
2	6.901	VV R	0.1040	8007.90674	1197.37476	97.9653
3	7.329	VB E	0.1134	16.89939	2.15666	0.2067
4	7.847	BV	0.0733	7.38698	1.55718	0.0904
5	8.288	BB	0.0963	21.90447	3.85179	0.2680

*** 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
```




```
================================================================================
                          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
```

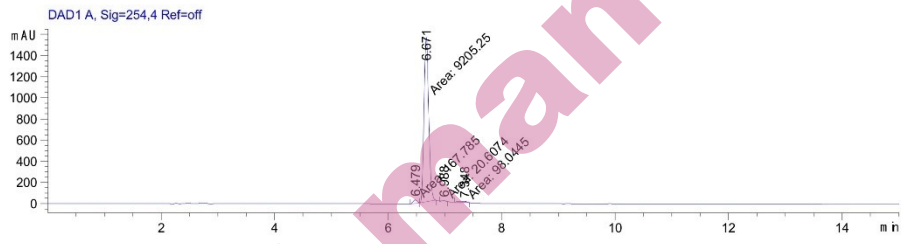
Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.621	BB	0.1206	76.21922	10.51346	1.4169
2	8.496	BB	0.1123	5272.46436	729.43896	98.0116
3	9.602	BB	0.0836	5.84354	1.18304	0.1086
4	9.891	BB	0.0962	24.90395	4.02220	0.4629
Totals :				5379.43106	745.15767	

```
====================================================================
                        *** 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.ACN.M (Sequence Method)
```

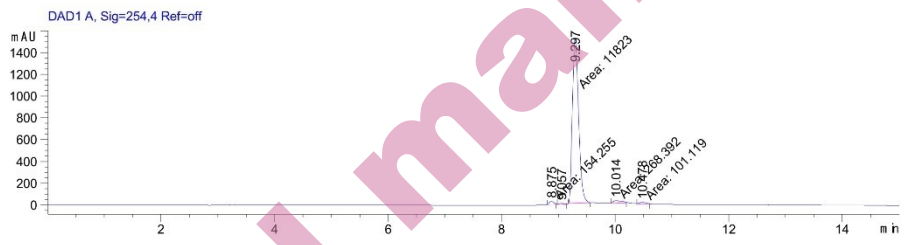



```
======================================================================================
                              Fraction Information
======================================================================================
No Fractions found.
======================================================================================
======================================================================================

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

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

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

Peak RetTime Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   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 Type  Width     Area      Height     Area
  #   [min]        [min]   [mAU*s]     [mAU]       %
----|-------|----|-------|----------|----------|--------|
   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

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

6. REFERENCES

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